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AGRANULOCYTOSIS: ITS ETIOLOGY AND TREATMENT*

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IN the past few years the condition known as agranulocytosis has apparently become much more common, both in this country and abroad. Its dramatic symptoms and signs, together with its high mortality rate, have brought the disease into sharp relief and have resulted in the occasional expression of clear-cut opinions as to its treatment and its etiology which are not, in all instances, entirely justified. In spite of our recently acquired familiarity with the disease, it still remains a mystery in many respects.

Certain authors[1, 2, 3, 4, 5], regard the disease not as a clinical entity but rather as a syndrome common to many pathological conditions and their view may yet be proved correct. Before this question can be definitely answered a large number of cases must be carefully studied both from a clinical and a pathological point of view. One cannot reach a clear-cut decision from either alone. Rose and Houser[2] give a number of arguments in support of their belief that agranulocytosis is not a specific entity and their reasoning is similar to that of many others who hold the same view. Leukopenia occurs, they say, under many conditions. Yet the fact that anemia occurs under many circumstances does not militate against the fact that pernicious anemia is an entity. They point out that there is no known etiological agent for agranulocytosis and that the condition has not been exactly reproduced in animals; yet it does not follow from these facts that there is no such disease. The etiology of myelogenous leukemia is unknown, nor has it been exactly produced in animals. One cannot by such arguments so easily dispose of this difficult question.

That extreme leukopenia and neutropenia alone do not constitute valid criteria for the establishment of a single disease should be obvious. Many authors have properly pointed out that hematological pictures similar to that seen in agranulocytosis may be found in many diverse conditions[3, 6, 7, 8, 9]. Yet because one disease may easily be confused with others does not argue that the first is not an entity.

Brogsitter[3], in a consideration of "agranulocytosis," lists thirty-four patients with marked leukopenia and granulopenia in which the hematological picture was directly traceable to some other definite underlying condition. But it is noteworthy that 50 per cent of these were males, that in nineteen there was notable anemia and that in 78 per cent of the cases having adequate data, the platelets were markedly diminished. These are not findings common to true agranulocytosis.

Doan[9] believes that only 20 per cent of the cases referred to his clinic with leukopenia could properly be regarded as falling into the narrow classification of true agranulocytosis, while Mettier[10], in a study of 1,167 cases of leukopenia, found only 6 per cent which were not explainable on the basis of some well-recognized disease, of which the leukopenia was but one striking sign. Moderate leukopenia is seen in the course of many infections; extreme leukopenia may occur as a sequel to overwhelming sepsis; it is seen as a result of benzol poisoning and may be due to the toxic effect of gold, bismuth or arsenic; it is a prominent feature in aplastic anemia; it is not uncommon in severe pernicious anemia and is occasionally seen in both acute and chronic leukemia. There is no question but that the majority of patients with leukopenia have some well-recognized fundamental disorder to account for this hematological abnormality and further that this disorder is in some instances quite unrelated, primarily, to the hematopoetic system. Lack of appreciation of these undoubted facts necessarily leads to false thinking as regards the etiology, the nature, the prognosis and the treatment of the disease or syndrome under present consideration. The dramatic intensity of the symptoms of agranulocytosis should not blind us to the chaotic stage of our present knowledge of the disease. The intensity of the leukopenia is no criteria of the specificity of the disease in question.

Acute leukemia in the aleukemic phase very closely simulates agranulocytosis and the two diseases are not infrequently mistaken one for the other[11, 12, 13, 14]. In fact, for the present, the relationship of the two conditions must be regarded as problematical. Yet there would appear to be certain essential differences. Absence or marked diminution of platelets, anemia of moment, particularly if progressive, hemorrhages, especially from the mucous membranes

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of the mouth, notable enlargement of the spleen and enlargement of lymph nodes, not readily explainable by adjacent ulceration and infection, all bespeak the diagnosis of acute leukemia. In acute leukemia, especially in adults, the blood smear shows a considerable number of very immature cells; often virtually all the white blood cells are stem cells (blasts) and it is only in the most atypical cases that young forms are few in number. An occasional stem cell may be found in the blood of patients suffering from agranulocytosis. Any very considerable number, however, indicates the probability of leukemia and the more there are the greater the probability. A level is reached, which if more than temporary, almost certainly means leukemia. During convalescence from agranulocytosis there may be, and in fact usually is, a transient outpouring of myelocytes, but this stage is soon passed and clinical improvement is coincidentally evident.

Leukemic patients with temperatures of 102° to 104°F. may seem comparatively well. This is rarely the case with agranulocytosis. In this latter disease such temperatures are almost invariably accompanied by marked prostration and symptoms of toxicity. In agranulocytosis the fever is either steady or, more commonly, fluctuates within certain definite, rather narrow limits. In acute leukemia the temperature curve is often an extremely variable one. Afebrile periods are not rare, even at the height of the disease. It must be emphasized again that the total white count is of no vital importance in the diagnosis of leukemia, for leukemia is still leukemia whether the white count be 500 or 50,000 per c.mm. The character of the white cells, the concomitant alterations in the red blood cell and platelet picture and the pathological changes in the bone marrow determine the diagnosis and serve, at least in the majority of instances, to mark the one from the other disease. Acute leukemia, furthermore, is the more likely the younger the patient and it is probable that the majority of extreme leukopenias in children are traceable to leukemia or to some serious disorder of the myeloid system other than true agranulocytosis. We have never seen a case of agranulocytosis under the age of twelve years.

The distinction between the two conditions becomes still more difficult when one considers these patients who have had what appears superficially to be agranulocytosis, have recovered, either spontaneously or following some form of therapy, and have later succumbed to classical acute leukemia, proved by autopsy. Some years ago we published[18] a report of the case of a man suffering from marked leukopenia and granulopenia who temporarily recovered following intravenous nucleotide therapy, only to succumb to classical leukemia of a fulminating type four months later. The postmortem sternal bone marrow was characteristic of acute leukemia. It would have been of the greatest interest to know what the bone marrow showed during the initial seizure from which he temporarily recovered. Was this attack true acute leukemia with complete, though temporary, recovery or was it atypical agranulocytosis with the subsequent development of the even more fatal acute leukemia? These questions cannot yet be answered. Since that time we have seen two other similar cases. In each there was extreme leukopenia, moderate anemia, fever, thrombopenia, ulcerations and fever. In each, apparent recovery took place following pentnucleotide therapy, only to be followed by death from obvious and proved acute leukemia some months later. Brogsitter[3] has noted similar cases and he questions whether agranulocytosis and acute leukemia may not be different manifestations of one and the same disease. In the typical case it is not difficult to distinguish agranulocytosis from acute leukemia, but it must be admitted that in many instances the differentiation may be impossible.

It should also be remembered that chronic leukemia of any of the three types may, on rare occasions, become aplastic in the terminal stages. In one instance which came under our observation a classical chronic myelogenous leukemia, proved by sternal puncture, became aplastic in a matter of weeks and died with extreme leukopenia and granulopenia. In this case postmortem examination revealed little or no evidence of leukemic infiltration of any of the organs. Other instances of the same sort have come to our attention. In one (B. C. H. A-32-13) the patient had a white count of 240,000 per c.mm. and a blood smear characteristic of chronic myelogenous leukemia. Both liver and spleen were grossly enlarged. A month later, shortly before death, his white count had fallen to 1200 per c.mm. and no granulocytes whatever could be found. At autopsy neither liver nor spleen showed evidence of leukemic infiltration and the bone marrow in many places was completely aplastic. Only here and there could one find small areas of typical leukemic infiltration. The effect of such dilemmas on our diagnostic and therapeutic efforts are obvious.

Those cases showing very low red counts depart more obviously from true agranulocytosis. The lower the red count the less likely the disease is to be true agranulocytosis. With marked anemia, pancytopenia or pernicious anemia with an unusually low white count is the more likely diagnosis, but in certain instances the white cells in the peripheral blood of patients with pancytopenia fall far more rapidly and to a much greater extent than do the other formed elements and if sepsis should ensue one may have, as in one of our cases, a picture closely resembling true agranulocytosis. However, this

condition can be distinguished as a rule from agranulocytosis by the paucity of platelets, the progressive anemia, the presence of at least a few neutrophils in the peripheral blood and the tendency to bleeding from the mucous membranes. Yet, as with aleukemic leukemia, there may arise great difficulties and it is well within the realms of possibility that one disease may shade into the other.

Bearing in mind these diagnostic and nosologic difficulties it does seem, however, that, after discarding the extreme leukopenias secondary to sepsis, aleukemic leukemia, aplastic anemia, pancytopenia and leukopenias of certain metastatic bone tumors, arsenic, gold and benzol poisoning, there remains what for lack of a better term may be called agranulocytosis, agranulocytic angina or idiopathic malignant neutropenia. It is of this condition that we speak. The hematological picture, clinical course and pathological findings probably entitle it to consideration as an entity.

ETIOLOGY

The majority of the earlier authors regarded agranulocytosis as a direct result of overwhelming infection. (Brogsitter[3].) Yet gradually this point of view has been changing and there would seem to be considerable evidence that sepsis is not the cause, but rather the result of the disease. That such is the case is attested to by the fact that the white count has been found by many authors to be lowered for several days before any clinical signs or symptoms have been manifest. In one patient of ours the white count was 500 per c.mm. or lower for four days before the appearance of any clinical signs or symptoms whatsoever. On the fifth day the patient had an abrupt rise of temperature to 104°F., chills, headache, prostration and severe sore throat. Bacteria had successfully invaded a defenseless organism. It is difficult to envision an infection so potent as to virtually abolish leukopoiesis without at the same time giving rise to some other outward and visible sign or symptom. It is more logical to assume that the depletion of the available leucocytes renders the organism liable to infection of a most virulent sort. This belief has been frequently expressed[7, 8, 9, 12, 16, 18]. Furthermore, in those instances in which infection appears to be the true cause of the leukopenia, the differential white count and the histological picture in the bone marrow are quite different from that seen in agranulocytosis. One of us[8] formerly expressed the opinion that overwhelming sepsis might, and often did, give the picture of complete agranulocytosis. Further experience has led us to believe that it rarely does so unless there be some underlying bone marrow dyscrasia. In overwhelming sepsis the total peripheral white count may indeed be very low but polymorphonuclear neutrophils usually form a large percentage of the remaining cells. Myelocytes and young polys are common, even at the height of the leukopenia. In the unusually active bone marrow all stages of myelopoiesis are seen. Such a pathological picture is never seen in agranulocytosis when the disease is at its height. In this condition the neutrophils virtually disappear from the peripheral blood and in the bone marrow no forms more mature than stem cells, or at best promyelocytes, are seen unless there has already been blood regeneration and the patient has died of some complication, as is occasionally the case. These pathological changes will be referred to in more detail later.

Overwhelming infection can in all probability be discarded as a common cause of true agranulocytosis. That it may be an occasional cause need not be denied.

Allergy has been suggested by Pepper[7] as being of etiological importance in agranulocytosis and we have seen cases develop following the administration of antitoxins and sera of various sorts. But that allergy is of major etiological importance has yet to be shown.

That some endocrine disturbance is the basis for the condition is suggested by the fact that in many instances the onset of the disease occurs at the time of menstruation[19, 20]; and the well-known case reported by Thayer and Hansen-Prüss[21], in which attacks occurred regularly for over twenty years at approximately twenty-five day intervals, would seem almost certainly to be of glandular origin. It is doubtful, however, whether any very large percentage of the cases may be definitely traced to an endocrine disturbance. Thayer's patient appears to be unique and the fact that many female patients suffer from remissions or attacks at the onset of their catamenias does not necessarily lay any very solid foundation for an endocrine etiology of the disease.

The fact that agranulocytosis has increased markedly in recent years, together with the known leukotoxic effect of the benzene ring, makes most tempting the theory that some, if not all, cases are due to the administration of amidopyrine and allied drugs, therapeutic agents which have lately become more and more widely used. Madison and Squier[22] cite fourteen cases of apparently true agranulocytosis in which amidopyrine, alone or with some other drugs, was used in considerable quantities immediately before the onset of the disease. Hoffman, Butt and Hickey[23], Watkins[24], and others have drawn attention to a similar relationship between these drugs and the disease. Seemann[25], however, noted that in thirteen of his thirty-six cases amidopyrine or its allies had been taken, yet in fifteen there was definitely no history of such therapy. Similarly Jackson[26], in an analysis of twenty-seven of their cases in which complete and unequivocal data relative to medication were

at hand, found that in only seven of them could the disease be properly regarded as directly traceable to the administration of these compounds.

There can be no question but that amidopyrine or its allies are of etiological importance, particularly as Madison and Squier[22] have produced with these drugs mild and transient, but definite, granulopenia in patients who had recovered from a classical attack. But there is also no question but that in many other instances there is no such explanation of the cause of the disease. Furthermore, it has been pointed out that the drug may be taken in considerable amounts prior to the onset of the disease yet on careful analysis it may appear that it is of no etiological importance whatsoever. Eight of the twenty-seven cases studied by Jackson[26] had taken amidopyrine or allied compounds in considerable quantities, yet it could be shown in these instances that the therapy had not the slightest causal relation to the actual disease. The "post hoc ergo propter hoc" argument is notoriously fallacious. Andersen's[27] patient took lecalgin for one and a half months prior to the onset of granulopenia and the disease might well have been attributed to this compound. Yet recovery took place in spite of an increased dosage of the same drug. That these chemicals are of some etiological importance is undeniable, but they certainly are not the sole cause of the disease. A special report of the Council on Pharmacy and Chemistry of the A. M. A.[28] concludes that there is "no question that amidopyrine is very important in the production of granulocytopenia". The report does not say, nor does it imply, that all cases are due to the drug, nor does it preclude the possibility that there may be some preëxisting bone marrow dyscrasia which affords a fulcrum upon which the drug may work.

In a similar manner dinitrophenol has been shown to be the apparent cause of the disease in certain instances. (Bohn[29], Davidson[30], Dameshek[31], and Silver[32].) This drug, therefore, must also be regarded as potentially dangerous, even in therapeutic doses.

A familial tendency is rarely seen, yet in our series six patients had very near relations who had recently died of the disease. Chance alone may well account for this.

When all is said and done it must be confessed that the etiology of this disease still remains, in large part at least, obscure. That some cases appear to be caused by the administration of certain chemicals or by the action of certain toxins should not be regarded as indicating that the disease is but a syndrome. Pernicious anemia may be due to lack of an intrinsic factor, to radical surgical interference with the gastro-intestinal tract or to malignant disease preventing the proper functioning of such factors as cause a proper maturation of the red cells. In a similar manner a variety of agents, known and unknown, may prevent proper maturation of the granular white cells and so produce the disease agranulocytosis.

PATHOLOGY

The pathology of the disease is in dispute. Much of this confusion arises from failure on the part of many even to attempt the differentiation, either clinically or pathologically, of the various conditions giving rise to the striking but far from pathognomonic sign, that of extreme granulopenia. Confusion also arises from too great reliance being placed on the interpretation of stained smears taken from the bone marrow. Such smears are of importance in identifying certain cells not easily recognized in sections stained with eosin-methylene-blue. But from smears of the bone marrow one gets absolutely no idea of the number or arrangement of the cells and upon such factors, as well as upon the nature of the individual cells, the diagnosis of any marrow lesion must be based. Custer[33], and Peabody[34] have expressed the same opinion. Finally, confusion often arises from failure to recognize the normal variations of cellularity from bone to bone in adult life. To pronounce the bone marrow "aplastic" from an examination of the tibia alone is a display of complete ignorance of the normal findings.

Roberts and Kracke[18] say "there is a unanimity of opinion that the essential pathology (of agranulocytosis) is a marked and practically complete hypoplasia of the myelocytic tissues." In one of their cases, sternal puncture (smears) showed a "marrow entirely devoid of granular cells of any type, including even myeloblasts". In the photomicrograph illustrating this feature one would be at a loss to identify any cell. Dodd and Wilkinson[35] state that the bone marrow is aplastic, but it should be pointed out that they describe the marrow of a colored girl of eleven years with hereditary syphilis who after treatment with sulpharsphenamine developed extreme leukopenia. The condition can hardly be regarded as one of true idiopathic agranulocytosis. Schultz, himself, is often quoted as believing the marrow to be aplastic. Yet Leon, who described the marrow in Schultz's cases, merely says[36] that there were neither mature neutrophils nor myelocytes to be found and that the femur was partly red, partly fatty. Such statements cannot be construed as indicating that the author considered the marrow "aplastic". In other instances when the marrow is said to be aplastic, examination of the original source discloses the fact that in the case under consideration the tibia or mid femur only was examined. It is not surprising, therefore, that the histological picture of the disease is regarded as confusing.

Jaffé[37] found a bone marrow rather more cellular than normal with signs of marked degeneration in the granules of the myelocytes. These granules were said to "fuse with the cytoplasm". It would seem that under those circumstances it should be difficult to recognize them as granules, and without at least nonspecific granules, cells cannot be properly called myelocytes. Jaffé believed the majority of the white cells to be myelocytes with a moderate or considerable number of plasma cells and lymphocytes. Megakaryocytes he found in normal or increased numbers. Fitz-Hugh and Krumbhaar[38], in a most important contribution, postulate a maturation arrest at the stem cell stage with the added possibility of an end stage which might be regarded as aplastic. With this view we entirely agree.

After an examination of the marrow from twenty-five cases dying in various stages of what seemed clinically and hematologically to be classical agranulocytosis, it appears that the following generalizations could be made. The marrow of the vertebrae, ribs, sternum and mid femur were essentially the same. The degree of cellularity was usually normal. Rarely the femur remained fatty, as in the normal adult. It would seem that in these instances death occurred too soon for the marrow activity to spread peripherally, although this view cannot be advanced with any enthusiasm. In some sternal and vertebral marrows, particularly in patients dying later in the disease, a certain amount of hypoplasia existed. On the other hand in the fulminating cases the marrow was perhaps unusually rich in cells. The degree of cellularity, however, varied but little and is, we believe, an unessential feature of the condition. There was little or no disturbance in the red cell series. Erythroblasts, normoblasts and nucleated red cells occurred in normal or slightly increased numbers and showed no abnormal features. The megakaryocytes also were found in the usual numbers and histologically appeared perfectly normal. With this latter finding, Rotter[39] and Jaffé[37] agree. This is important in view of Roberts and Kracke's opinion that the hemorrhagic tendency which they regard as a very common symptom of the disease may be traced to a "marrow disfunction involving megakaryocytes and a decrease of platelet formation". We found not the slightest evidence in any of our twenty-five cases of such dyserasia.

The most marked bone marrow changes naturally occurred in the cells of the granular series. No mature granulocytes, either neutrophils or eosinophils, were found in any marrow, nor were there any true myelocytes. Very rarely a promyelocyte was seen. Practically every cell belonging to the granular series was a stem cell. Occasionally, to be sure, the peripheral blood picture had in part recovered and the patient had died of pulmonary embolus, sepsis or some other complication and in these instances, naturally, myelocytes, metamyelocytes and young neutrophils were found in profusion throughout the bone marrow which was generally hyperplastic; but, in those cases which, at the time of death, showed extreme leukopenia and granulopenia, only stem cells, plasma cells or lymphocytes were found. That this may be construed as a maturation arrest (Fitz-Hugh and Krumbhaar) rather than failure to deliver, is evidenced by the fact that the parent cells were often in active mitosis. These stem cells seem to be able to produce their own kind in profusion. Further maturation is denied.

In those patients who survived the ravages of infection for a considerable period (eight to twenty days) the bone marrow picture was somewhat different. It was then found to be relatively hypoplastic. Gradually as the disease progressed the stem cells diminished in number and their place was taken by lymphocytes and plasma cells and in cases dying as late as the fifteenth day after the apparent onset of the disease these cells constituted virtually the only white cells in the marrow. In general Rotter[39] agrees with these findings. This late stage would appear to correspond to the terminal "aplastic" stage postulated by Fitz-Hugh and Krumbhaar[38]. Phagocytic macrophages were at all times present in considerable numbers, particularly in the late stages of the disease. Such cells have also been remarked upon by Lichtenstein[13]. In no case did we note the degenerative changes referred to by Pepper[7] and Oppikofer[40], and so strongly stressed by Jaffé[37]. It is possible that when these changes do occur they are the result of bacterial invasion of the bone marrow itself. It is certain that poorly fixed or improperly stained marrow gives the impression of degeneration. Only by the most careful technic can such be avoided.

It must be recognized that until further work is done we cannot speak dogmatically of the pathology of a disease, the nature of which is still obscure. At present we would agree with Fitz-Hugh and Krumbhaar's view of a maturation arrest with a predominance of lymphocytes and plasma cells in the more advanced cases. A detailed study of these marrows will be published shortly.

CLINICAL PICTURE

The classical clinical description of complete agranulocytosis has been repeated so often[3, 7, 8, 12, 13, 17, 16, 18, 41, 76], that it hardly needs repetition here. We do not propose to enter into detail concerning the clinical picture, but rather to discuss such aspects of it as are at present under discussion or dispute. In general it may be said that the disease is characterized by a

rapid or sudden onset, marked prostration, fever, headache, malaise, chills, sore throat, ulcerative lesions of the oral cavity and gastrointestinal tract and extreme leukopenia and neutropenia, unaccompanied by notable anemia.

Most authorities agree that in the true disease, agranulocytosis, there is little or no material alteration of the red blood cell picture, or any notable diminution of the platelets[1, 13, 16, 39]. It must be recognized that a slight degree of anemia is not uncommon for various reasons in middle-aged or elderly persons and, therefore, may well be an incidental finding in true agranulocytosis. But for the present, at least, it is wise to exclude from this latter category those cases with marked anemia. Marked anemia does not often occur in agranulocytosis, nor does notable thrombocytopenia.

The disease occurs in women far more commonly than it does in men. Hueber[1] found 3.5 times as many women as men. In Lichtenstein's series[13] there were twenty-four females and three males. In our own series of 103 cases*, eighty-three were female, twenty were male. These cases were so far as possible limited to such as might properly be called true agranulocytosis. Thus there can be no question but that the female sex is far more often affected than the male.

Agranulocytosis occurs most commonly in mid-adult life. The peak appears to come in the fifties, 29 per cent of our cases occurring in this decade. None of the 103 was under ten years of age and only two were over eighty. Lichtenstein[13], and Fitz-Hugh and Comroe[76] found approximately the same age distribution. We cannot agree with Beck[17], that practically every case occurs between forty-one and fifty-eight.

The white count is rarely as high as 2500 per c.mm. and is often 1000 or less. Frequently it is in the hundreds. In this series of 103 cases, thirty had white counts less than 500, twenty-eight had white counts between 500 and 1000, thirty-eight had white counts between 1000 and 2000 and only seven had white counts of between 2000 and 3000. Neutropenia of an extreme grade is the rule. Only seven of our cases showed neutrophils of over 5 per cent at the height of the disease. It is noteworthy that eosinophils are rather consistently absent, not only during the disease but often for months afterwards. This might be taken to argue against an allergic basis for the condition. Such neutrophils as remain are old and often degenerated. The majority of the white cells present are lymphocytes, for the most part of the adult type and showing no noteworthy abnormalities. An occasional young lymphocyte may be seen. The monocytes may, in certain instances, be present in abnormally high percentages. Some authorities believe that when this occurs the prognosis is favorable, but there is little evidence to support this view. Rarely a few stem cells may be seen, but never in the quantity that are found in acute leukemia. This very important point has already been referred to.

In our experience and that of Lichtenstein[13], Kastlin[16], Schultz and Jacobowitz[42], Millman and Furculo[43], and others the platelets are normal during the acute attack and often markedly increased during convalescence. Aubertin and Lévy[5], find, on the other hand, a constant thrombopenia and Roberts and Kracke[44] believe that the platelets are markedly reduced. We have seldom seen marked thrombopenia in true idiopathic agranulocytosis and such a finding should, in our opinion, be regarded as an indication that some other disease, notably aplastic anemia or acute leukemia, is under consideration. Only recently a case classical in all ways of agranulocytosis except for marked thrombopenia showed at autopsy classical acute leukemia. Possibly the constant thrombopenia found by Aubertin and Lévy[5] is to be explained by their view that "L'agranulocytose proprement dite n'est q'un des aspects particuliers d'un syndrome plus général qu'on retrouve isolément, ou en association avec les autres grands syndromes de la pathologie sanguine parmi lesquels il mérite de prende place." No attempt has apparently been made by these authors to differentiate accurately those varied pathological states characterized by extreme granulopenia. Not all macrocytic anemias are pernicious anemia "proprement dit".

Roberts and Kracke[44] stress the commonness of bleeding in true agranulocytosis and state that it is "rare to see a case in which there is not some manifestation of the hemorrhagic trend". Most authors point, on the contrary, to the rarity of hemorrhage and with this latter view we heartily concur. Kastlin[16] found hemorrhagic tendency clinically in but eight of his forty-three cases. Lichtenstein[13] regards hemorrhages clinically as extremely rare. Manifest bleeding during life, especially from the mucous membranes, is strong evidence that one is dealing with some form of acute leukemia. This latter disease may occasionally be of such a fulminant nature that death occurs (with coincident sepsis) before definite anemia sets in. It must be remembered that the life of the mature red cell in the peripheral circulation is in the neighborhood of three weeks. Destructive invasion of the marrow with consequent sepsis and death may well occur inside this period.

Jaundice was regarded almost as a sine qua non by Schultz[45], and Pepper[7] states that it occurs in one half of all cases. Kastlin[16] also

*These patients were either seen personally or reported in detail by various physicians throughout the country. For the continued coöperation of these physicians we are deeply grateful.

found jaundice in seventeen of thirty-two cases. Chalier[46] believed jaundice to be common but secondary to infection and Lichtenstein found jaundice in but eight of twenty-seven cases. In our own series of 103 cases jaundice was noted in but seventeen instances. From the pathology of the disease there would seem to be no very good reason for supposing jaundice as a natural concomitant of the condition and this symptom, when found, is more properly to be regarded as the result of hemolysis due to secondary bacterial invasion. Indeed, it cannot otherwise be adequately explained.

The spleen is but rarely obviously enlarged, never greatly so. Gross enlargement of the spleen bespeaks leukemia.

The ulcerations and gangrenous lesions may be found in almost any part of the body; rarely they may be absent. In our series they were most common, or at least most prominent, in the throat and pharynx, but such lesions are not at all uncommon in the vagina, rectum, skin and gastrointestinal tract[13, 39, 47, 48, 49]. Many cases are admitted under the guise of diphtheria to hospitals for contagious disease. (Gordon and Litvak[50].)

Gangrene and consequent sloughing may occur; this is a particularly dangerous event when it occurs in the gastrointestinal tract. Two patients in this series died from rupture of a necrotic intestine. In one the blood picture had already become normal, too late, however, to be of avail.

Owing to the absence of neutrophils there is none of the usual inflammatory reaction about the ulcerations, but a peculiar brawny edema may be most extensive and in the throat constitutes a grave menace to the patient's life. This edema may be so great and so extensive as to preclude the possibility of swallowing and render breathing well-nigh impossible.

The fever has nothing characteristic about it. As a general rule the temperature reaches a maximum of 103° or 104°F. Rarely it may rise to 106° or even 107°F. In some patients only a very moderate hyperpyrexia is the rule. A steady, high, unremitting temperature is of extremely grave prognostic import.

TREATMENT

The treatment of any disease, the pathogenesis and nature of which is uncertain, is at best unsatisfactory and the more so when that condition may be easily confused with other pathological entities of probably a different fundamental nature. Many measures have been advocated to combat agranulocytosis. None is specific. Almost all authorities agree that the major problem is that of restoring the bone marrow to its normal activity and thus raising the peripheral white count; for the loss of leucocytes removes one of the body's great defenses against infection. Without bone marrow recovery, there can be no cure.

Non-specific therapy, such as the injection of sterile milk or turpentine, is conceded by almost everybody to be useless. That one gets a white cell response in normal patients by such therapy is not the slightest reason for supposing that a similar response should occur in agranulocytosis. The probable effect of such treatment in patients with normal bone marrows, is chemotactic, that is the calling forth of such mature and slightly young polys as are already available in the bone marrow, and their rapid and efficient replacement. There are no neutrophils in the bone marrow of agranulocytosis patients to call forth.

Transfusion of blood has been endorsed by some[1, 7] and without question recoveries have followed one or more such transfusions. Aside from this fact there is not good evidence that blood transfusions have a stimulating effect on the bone marrow or a curative effect in agranulocytosis. Indeed, it is not an uncommon experience to find the peripheral white blood definitely lower after transfusion than before. The number of white cells actually given the patient is small; their life is short; and, furthermore, the patient, as a rule, does not need either plasma or red cells. In our series treated with Pentnucleotide (N. N. R.), the mortality in those patients receiving transfusions was exactly the same as that of those who did not. In the presence of sepsis when the white count has risen to normal or abnormally high levels, small multiple transfusions may be of value. There seems to be little convincing evidence that they tend permanently to raise the white count or stimulate the marrow.

Stimulating doses of x-ray were advocated by Friedemann and Elkeles[51]. They treated forty-three patients. Of these, twenty-three had either sepsis or pneumonia or died within thirty-six hours and all were discarded by the authors in so far as evaluating the effects of treatment was concerned. Of the twenty remaining "cases" there appear to be but seventeen individuals and of these eight died, a mortality of 47 per cent. It should be recorded for the accurate comparison of mortality statistics that in the complete unexpurgated series the mortality was 82 per cent.

Taussig and Schnoebelen[52] treated four cases by x-ray with a mortality of 50 per cent. Hueber[1] unenthusiastically recommends radiation. Reznikoff[53] has expressed the opinion, and it is ours as well, that even small doses of x-ray tend to depress the marrow and he points out, quite properly, that four or five days must elapse before the effects of any maturant agent can be seen in the peripheral blood. It is usually claimed by those who advocate radiation therapy that hematological changes of a favorable sort were seen in the peripheral blood in a few

hours. When such changes have occurred one is tempted to believe that the rise was spontaneous, or, if actually due to the radiation, was a redistribution phenomenon rather than a genuine stimulation of a dormant or suppressed marrow. Pepper[7] is not enthusiastic about radiation therapy. Lichtenstein[13] treated twenty cases with improvement in seven, but a year later only two were alive, giving a mortality of 90 per cent. Of the cases in our series only three received x-ray (as well as Pentnucleotide). All died. A critical analysis of the results of radiation therapy does not seem to afford any very convincing evidence of its value.

Some students of the problem, notably Roberts and Kracke[18], believe that "sepsis and necrosis are the great hope of every patient with complete granulopenia". This hope is only too often fulfilled. These same authors, however, say that "with sepsis there is death unless the granulocytes reappear". The implication appears to be that sepsis and necrosis in and by themselves stimulate the bone marrow to regeneration and thus restore the leucocytes to the peripheral circulation. It is difficult to prove that such is not the case, yet it would seem very unlikely. That sepsis raises the white count in individuals possessing a normal marrow is no indication that it will do the same in one whose bone marrow contains, so far as white cells are concerned, only stem cells. Just how sepsis causes leucocytosis and a hyperplastic marrow in normal patients is not clear. There is no evidence, however, that it does so by stimulating the few preëxisting stem cells to maturation. The sepsis of agranulocytosis is admitted by all to be the result (not the cause) of the leukopenia. All who have had any wide experience with this disease have seen cases in which the peripheral white count has risen coincidentally with the development of abscesses. It does not follow that the abscess caused the hematological improvement. No one has suggested deliberately giving pyogenic organisms intramuscularly as a therapeutic measure. It is common to see the white count rise coincidentally with the development of the outward and visible signs of sepsis and, if the peripheral blood be carefully followed in these cases, in many instances there will be found a sudden drop of leucocytes as the formation of the abscess begins, to be followed again, in a matter of hours or days, by a prompt rise to the previous or an even higher level. The bacteria have been present all along, but no white cells have been available. "Laudable" pus could not be formed; no "abscess" could develop. The return of bone marrow activity supplies these militant cells and they have been immediately drawn to the site of infection, thus temporarily depleting the supply in the peripheral circulation. Hence the transient fall in peripheral white count. The blood must be followed hour by hour to detect these changes.

Furthermore, agranulocytosis has developed in the presence of preëxisting and patent sepsis. Millman and Furculo's[43] patient "was stricken in her second attack during a time when she was suffering from two abscesses in the gluteal region. This would tend to indicate that in this case, at least, abscess formation which has been advocated as a method of treatment of agranulocytosis was of no benefit". Of the thirty-five cases in our series on which blood cultures were taken, thirty had sterile blood and of these nine died. Five had positive blood cultures and of these three died. The evidence that sepsis and necrosis in cases of agranulocytosis bring about a regeneration of the marrow is not convincing.

Liver extract has been advocated by Foran[54]. He injected the "equivalent of 100 grams of liver into the vein or muscle every 8 to 12 hours until a definite rise of total white count—" had taken place. Four cases of apparently true agranulocytosis were successfully treated. Yet Coggeshall's[55] case failed to respond to six vials of liver extract (Lilly 343) intravenously each day. Four of the patients in our series received liver extract as well as Pentnucleotide. All died. It may be argued that insufficient liver was given. The same would apply to the Pentnucleotide. Silver[32] treated a case of agranulocytosis due to dinitrophenol with liver without beneficial results. Bonsdorff[56] treated two cases with liver intravenously with recovery in both instances. There seems to be no reason to doubt, however, but that the first patient was suffering from pernicious anemia. She had a red blood cell count of 528,000 per c.mm., a color index of 1.32 and a white count of 1,750. His second patient had extreme leukopenia apparently due to novarsenobenzol and bismuth. The withdrawal of these drugs may well have had as beneficial an effect as the liver extract. Bonsdorff argues that, because the white count rises in pernicious anemia following liver therapy, it should also rise in agranulocytosis. Yet the mechanism of the leukopenia of pernicious anemia is as yet not clear. It may well be that it is similar to that which produces the anemia in leukemia, namely a crowding out of one series of cells by the overgrowth of another. If this be so, liver therapy would raise the white blood cell count in pernicious anemia by an indirect rather than a direct method. At present the ultimate value of liver therapy in agranulocytosis cannot be estimated. It can only be said that a few patients have been successfully treated.

In 1930 Reznikoff[57] advocated the use of *adenine sulphate* (one of the breakdown products of Pentnucleotide) in the treatment of agranulocytosis and in 1933[58] summarized the results in fifteen cases with eleven recoveries. He also treated eight cases in which the diagnosis was doubtful with but one recovery and twelve cases complicating other diseases with

two recoveries, and these but temporary. His conclusions in so far as pure agranulocytosis were concerned were conservatively optimistic.

In 1924[59] one of us definitely demonstrated the presence of pentose nucleotide in normal human blood. Inasmuch as it had been shown by Doan, Zerfas, Warren and Ames[60] in 1928, that such products could raise the peripheral white count in normal animals, it was decided to try the effect of this substance, presumably a normal metabolite of the intact and healthy organism, in those conditions characterized briefly by extreme leukopenia.

In 1931[61] we reported the results of such therapy in twenty cases of extreme leukopenia or neutropenia with fourteen recoveries. All of these cases might properly be considered as true agranulocytosis or the granulopenia secondary to sepsis. In 1932[62] we reported an analysis of sixty-nine cases (including the original twenty). In the total series the mortality was 26 per cent. Since then there have been added thirty-four cases, most of which have been under our direct supervision. Only those cases treated for less than forty-eight hours or those which died of some entirely unrelated disease were excluded. Such practice has been common in the compilation of data by other investigators. True complications, of whatever nature, did not, in our opinion, constitute valid reason for omitting the case from consideration and analysis. Each patient was counted but once, no matter how many remissions and relapses he may have had. If a patient recovered more than once and subsequently died of the disease, a death was recorded and a death only. All cases have been followed to date. The mortality in this entire group was 33 per cent.

Pentnucleotide (N. N. R.) may be given intramuscularly or intravenously. In the average case of agranulocytosis with a white count between 1000 and 2000 per c.mm., 10 cc. Pentnucleotide are given intramuscularly two, or preferably, three times a day until the white count has definitely risen and young neutrophils have appeared. This change usually occurs on or about the fifth day of treatment. Ten cc. are then given once a day until the white count has been normal for several days. In cases which are extremely sick, and especially in those in which the total white count is below 1000, 40 cc. should be given a day until the white count has definitely risen and young neutrophils have appeared. Fifty cc. may be given even more advantageously. The drug may also be administered intravenously well diluted in saline by the continuous drip method, the speed of injection being such that no untoward reactions occur. Usually 50 to 100 drops may be given a minute when 20 cc. Pentnucleotide are diluted in 1000 cc. of normal saline solution. The drug should be continued in large doses until the white count has definitely risen and in somewhat smaller amounts until it has been normal for several days. If there has been no response at the end of ten days, further therapy with Pentnucleotide is useless.

In most patients there are no untoward reactions to the drug. In some there is a transient sense of discomfort at the site of injection. In others there may be precordial distress, dyspnea or nausea. Very rarely are the symptoms alarming. If, however, they are sufficiently severe to upset the patient the individual dose may be reduced and the number of injections per day correspondingly increased. In this manner one can almost always give the required amount each day. It is useless, especially in severe cases, to give small doses. The drug should never be given to a patient with an anaphylactic history, nor to one with severe cardiac damage.

In favorable cases the first signs of improvement following Pentnucleotide therapy are evidenced by the appearance of myelocytes in the blood stream. (Doan[41].) These cells may reach 20 per cent of the total white cells. This change usually occurs on or about the fourth day following treatment and corresponds in certain measure to the reticulocyte rise in pernicious anemia. Shortly thereafter the temperature falls, the total white count rises and more mature neutrophils take the place of the immature cells.

Of the 103 patients treated in this manner, sixty-nine or 67 per cent, recovered and are still alive. Four additional patients recovered from their initial attack but died in a subsequent relapse. Thus the mortality (33 per cent for the entire series) is considerably lower than that generally accepted for the untreated disease, and considerably lower than that for any comparable series treated by any other measures. Taussig and Schnoebelen[52], in 330 collected cases, give the mortality as 76 per cent, and furthermore, they scored a recovery for each and every remission. The corrected mortality in their series would naturally be considerably higher. Brogsitter[3], in 1930, found a mortality of 77 per cent in sixty-four cases. Fuld[63], in 1930, noted recovery in but twenty-three cases out of 248, a mortality of 91 per cent. Uffenorde[48] found a mortality of 77 per cent in 1934. In 1934 Roberts and Kracke[44] stated, "Complete granulopenia is usually a fatal disease during the first or a later attack", and these authors say that they have not seen any of their recovered cases return to complete health. One of our patients is now a head nurse in a large obstetrical hospital, two are active practitioners of medicine and while it is true that convalescence is usually prolonged, yet certainly many cases return to an active normal life without any symptoms of note or any abnormalities in their blood picture. Rosenthal[64] reports ten cases

with five recoveries. It is to be noted, however, that, of these five, two had neutrophils over 20 per cent with total white blood cell counts of 4000 and over, and two more had neutrophils of 10 per cent with white blood cell counts of 1300 and over. The fifth case had 440 white blood cells per c.mm. with 5 per cent neutrophils. Such hematological findings would at least tend to indicate a good prognosis and it may well be questioned whether such cases should be regarded as instances of true agranulocytosis. (Brogsitter[3].)

Considerable stress, especially from the point of view of prognosis, has been placed upon the occurrence of "mild leukopenias". (Beck[17], Roberts and Kracke[18, 44].) That such indeed exist need not be denied, but the implications of their recognition have sometimes been more far-reaching than cogent. Roberts and Kracke[18] have found that one in every four patients has a leukopenia and neutropenia. They define leukopenia as a total white blood cell count of below 6000 per c.mm. and neutropenia as neutrophils below 67 per cent, and they set forth the theory that patients showing such leukopenia and neutropenia suffer more often from exhaustion, nervousness and weakness than do those with normal blood pictures. Yet the percentage of patients in their control group showing exhaustion, nervousness and psychoneurosis is almost identical with the figures of the "leukopenic" group and while twice as many of the granulopenic patients suffered from weakness as did the control group, yet mathematical analysis of these figures shows that such variations might well be attributed to chance alone. The relation of these findings to agranulocytosis is not at the moment clear. As Fitz-Hugh, in a discussion of the paper by Waters and Firor[65], says, "The —— statement about the —— finding that one in four persons shows a granulopenia should be accepted with caution. The convalescent leukopenia with relative lymphocytosis and a slight increase of eosinophils is an almost universal finding after the conquering of an acute infection." The granulopenias to which Roberts and Kracke refer are mild in degree. For the moment let it be said that we are not now concerned with patients whose total white count is in the neighborhood of 4000 and whose differential count shows 40 per cent neutrophils, but rather with what for lack of a better term has been called agranulocytosis, a disease characterized by extreme leukopenia and granulopenia. That mild cases of granulopenia exist is not denied. They have not, however, been included in our series of 103 cases. Only seven of these had more than 5 per cent neutrophils, seventy-four had no neutrophils whatever. Only seven had counts of 2000 or over, thirty had counts of 500 or less. It is important to distinguish sharply between those patients who have a white count of 4000 and one who has a white count of 1500. It may still be argued that the higher the white count, the lower the mortality and within certain limits this is true. Among the seven cases which had white counts of 2000 and over, the mortality was 16 per cent, whereas 19 per cent of those whose white counts were 1000 to 2000 died and of those whose counts were below 1000, 55 per cent died. It would seem that when the white count fell below 1000 the mortality was materially increased. Yet even this latter figure is considerably below the accepted figure of 75-85 per cent mortality of the untreated cases of agranulocytosis.

Pentnucleotide (N. N. R.) has been used with apparent success by many[9, 10, 11, 30, 36, 43, 49, 66, 67, 68, 69, 70, 72, 73, 74].

Zia and Forkner[75] have used it with considerable success in cases of agranulocytosis complicating kala azar. They say, "It would appear that the administration of pentose nucleotide or of purine bases offers by far the most satisfactory treatment, not only for agranulocytosis but also for conditions of agranulocytosis the result of pyogenic infection or of chronic benzene poisoning."

Others have had less success[56, 76, 77, 78]. In not all of these cases was the diagnosis true agranulocytosis.

It is impossible at present to evaluate properly the true usefulness of the drug. It appears to be harmless, even over long periods of time. The mortality of those cases treated with it, seems to be definitely lower than that in any comparable series treated by other means. Certain confirmatory evidence is brought forward by the extramedullary myelopoiesis which may be brought about by its injection into animals and the uniformity with which hematological improvement occurs about the fifth day of treatment. The possibility of spontaneous remissions must, however, always be borne in mind and in any individual case cannot be easily dismissed. Patients have received the drug in adequate amounts and recovered, only to relapse again with complete therapeutic failure on the second attempt. Patients have failed to respond to apparently adequate dosage and then recovered spontaneously. But the fact remains that no other therapeutic agent has been shown to be more efficient.

Thus four of the patients in our series who died received, in addition to Pentnucleotide, liver extract and x-ray therapy. Harkins[76], quoted above as being unenthusiastic about Pentnucleotide, used liver, iron, leucocytic extract, sodium nucleinate, adenine sulphate and guanine with indifferent results. Silver's[32] patient with 20 per cent neutrophils and 10 per cent monocytes died in spite of liver extract therapy. Zinninger's[77] patient, who failed to respond to Pentnucleotide, died two months later, having just "responded" to Addisin.

At present writing it would seem that Pentnucleotide, provided there are no untoward reactions, offers the best chance of recovery in a patient with true agranulocytosis.

It stands to reason that intelligent bedside care, careful nursing, adequate nourishment and fluids are all a necessary and obvious part of the treatment. The patient must be protected in so far as possible from infection, but to attempt to sterilize the ulcerated lesions by means of antiseptics is fruitless. Such constant therapeutic nudging serves only to keep the patient awake when he should be resting. But frequent washings of the mouth and throat with soothing solutions may allay the pain, reduce the amount of secretion and make the patient in general more comfortable.

It has been suggested (Beck[17], Roberts and Kracke[44]) that surgical intervention is contraindicated. With this view we heartily disagree. Such surgery should be undertaken as would be advised in a patient with a normal blood. Retrocecal abscesses have been drained (Lintz, J., Personal Communication), amputations of infected limbs have been effected (Thompson, W. P., Personal Communication), thoracotomy for empyema has been done, ischiorectal abscesses have been opened and a cervical cellulitis has been drained; in all cases rapid recovery has ensued. In one instance death was apparently due to lack of proper surgical intervention after the blood picture had become normal. There is no reason why surgical measures should not be instituted, provided they are clearly indicated, as they would be in other patients. An operation of election should, of course, be avoided.

It is certain that all drugs containing a benzene ring should be immediately and completely omitted. Madison and Squier[22] found 100 per cent mortality in their six cases which continued to take amidopyrine or its allies. Of the eight patients in our series who continued to take the drug during their attack, seven received Pentnucleotide treatment and six lived, but it should be pointed out that in only three of these instances was the benzene derivative regarded as causative. Two of these three patients received Pentnucleotide treatment and recovered completely. The third was not so treated and died. It would still appear to be the wiser course, however, to omit any such drugs as amidopyrine or its allies.

In certain instances, edema of the throat may be so great that deglutition and even respiration may be difficult or impossible. Tracheotomy may be tried in such instances, but in our experience it has been of no avail.

CONCLUSIONS

1. Whether agranulocytosis is to be regarded as a disease entity or a syndrome cannot as yet be dogmatically stated, but it is probable that such a disease entity does exist.

2. The etiology of the condition must, for the present, remain uncertain. Amidopyrine and its allies, however, may and probably do have much to do with the development of certain cases.

3. The pathological changes in the bone marrow of agranulocytosis consist of a maturation arrest at the stem cell stage. Later in the course of the disease plasma cells and lymphocytes replace, to a large extent, the previously existing stem cells.

4. Careful asepsis, adequate nursing and intelligent general care of the patient are obviously essential and important parts of the treatment.

5. Pentnucleotide (N. N. R.) intramuscularly or intravenously offers, at the present time, the best method of stimulating the bone marrow to recovery and the results following this therapy have been more satisfactory than those after any other type of treatment.

6. Until the nature, etiology and pathology of agranulocytosis is unequivocally placed upon a sound basis, the diagnosis, treatment and prognosis of the condition must remain *sub judice*.

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OVERCROWDING AND THE SPREAD OF DISEASE

Overcrowding is a prime characteristic of slum areas. The inhabitants have little money for rent and must, as a rule, live in quarters that do not fit the size of the family. This is especially true today, because of the doubling-up of families. We must distinguish between congestion in sleeping quarters, in the individual house or flat as a whole, in the halls used by several families, in the yards, or playgrounds, in the streets, in public buildings. It is recognized that "the maximum opportunity for the spread of infection will occur when a center of close aggregation is associated with marked dispersal." Thus it is regarded that the manifest excess of contact diseases in slum areas is due not so much to overcrowding in the individual flat or house as to the general congestion of the area—congregation of young children in the hallways of tenements and in the streets, etc. The problem is therefore a broad one; and it is evident that similar chances for the spread of infection occur throughout a crowded American city, in the subways, theaters, schools, etc.

Diseases which are passed from one to another on account of close personal contact are numerous, including the common cold, sore throat, bronchitis, influenza, diphtheria, scarlet fever, mumps, chicken pox, whooping cough, cerebrospinal fever, measles, and even pneumonia and tuberculosis. Although numerous means of conveyance are factors, these diseases are spread primarily by secretions from the mouth and nose through droplet infection.

Analysis of 3,200 deaths of infants under 1 year in a number of countries showed a higher proportion of deaths from infectious diseases where the housing was bad. Good housing, 34.7 per cent; moderately good, 40.4; bad, 45.9. It did not appear that this difference could be entirely due to "social status," since a corresponding tabulation by social status showed: Good, 33.9; moderately good, 40.6; and bad, 39.6.

In the case of the common communicable diseases of children (measles, diphtheria, scarlet fever, whooping cough), there is recognized to be an excess mortality in overcrowded districts of cities. The reason for this higher mortality would appear to lie in the lower age incidence, since these diseases are more fatal (i.e., have a higher case fatality), in the very young ages.

It would not be possible to refer to any proportion of studies made on the relation between density and mortality, from William Farr down to the present time. Interpretation of them is complicated by the difficulty of ascertaining what the real causal factors are, but the evidence is unmistakable that congestion and overcrowding do in themselves cause the spread of disease. Their effect in the past on the prevalence of such epidemic diseases as plague, smallpox, cholera, typhus fever, and influenza is almost beyond belief; but the point is to be made that such conditions cause a real menace in the slum areas at the present time. To-day, with our knowledge of the methods of spread of communicable disease, the continuation of such a menace is a severe criticism of our civilization. It should be added that in all programs of slum clearance or rehousing there must be a definite plan to prevent the development of equally hazardous conditions in other districts.

Communicable diseases endemic to slum areas are likely to be carried into other parts of the population. That has been a striking phenomenon in the past, especially in connection with those vast epidemics of smallpox, plague, cholera, and typhus fever in which so many millions of lives were lost. That the danger is not one of the remote past is shown in the epidemic of typhus fever and relapsing fever in Russia from 1919 to 1923. In 1920 about 5,500,000 cases were reported in European Russia and the Ukraine, while 13,000,000 were reported for the period 1919 to 1923.

Even in the United States to-day, no individual can feel that his personal health can be maintained independently of the public-health status of the population generally or of that of the less privileged groups.—*United States Public Health Service.*

NEW ENGLAND SURGICAL SOCIETY

BLEEDING GASTRIC ULCER*

BY GEORGE ALBERT MOORE, M.D.†

GASTRIC hemorrhage of the less severe types in which there is a gradual loss of blood or a small amount of acute bleeding is quite generally treated conservatively.

Massive gastric hemorrhage either in repeated attacks or continued bleeding under medical treatment is a grave emergency, frequently demanding surgical intervention. Gastric bleeding, varying from a slight stain to massive hemorrhage occurs in many diseases such as cirrhosis of the liver, splenic anemia, biliary diseases, chronic appendicitis, portal thrombosis, acute dilatation of the stomach, brain tumors and several others. A local lesion from which the hemorrhage originated, is seldom demonstrated except in diseases causing esophageal varices. Our interest in these patients after recovery from the acute symptoms is in the differential diagnosis and the method of treatment which will prevent a recurrence.

A rare type of gastric hemorrhage, of which little is known regarding the pathogenesis, presents a difficult problem in treatment. The typical case occurs in an apparently healthy young woman without preceding gastric disturbance, although it may occur in older women and in men. In some patients a history of insignificant gastric symptoms is obtained, possibly slight bleeding for a few days or weeks before the acute hemorrhage. A small number result from an acute infection, others are thought to be of toxic or anaphylactic origin. Laboratory and x-ray studies are negative. Gastroscopic examination has proved of considerable value in some cases as reported by Clerf[1] and Benediet[2]. Bortz[3] classifies these disorders as: 1. Diffuse gastric hemorrhage from physical or emotional strain. 2. Profuse hemorrhage from superficial defects in the mucosa, Dieulafoy's ulcer and Einhorn's disease. 3. Hemorrhage from pore-like openings in one of the gastric vessels. 4. Hemorrhage from multiple minute erosions. 5. Capillary oozing. 6. Hemorrhagic gastralgia.

The onset of acute bleeding is sudden, with hematemesis or melena, followed by faintness, collapse and the other usual signs of hemorrhage and shock. Many of these patients recover under conservative treatment after one or more attacks, others have repeated attacks with a fatal result; a small number are saved by surgery. Absolute rest in bed with sufficient morphine, withholding food and liquids by mouth and an icebag to the epigastrium are indicated in all cases. Glucose and saline intravenously and stimulants of any kind are contraindicated as they raise the blood pressure and tend to promote hemorrhage. Fluids should be administered by rectum and by hypodermoclysis. Various hemostatic drugs and serums too numerous to mention, atropine, alkalies, and the Jutte and Levine tube for lavage have been used. All are of questionable value, some are decidedly harmful. Blood transfusion probably has been used more frequently than any other method of treatment. Small amounts, i.e., 250 cc., are usually given to avoid raising blood pressure, though 500 cc. is advised in some clinics.

The unsatisfactory results of surgery in these cases are apparent from the various types of operative procedure reported. At operation and autopsy in many patients no lesion of the gastric mucosa is found after prolonged search. In others, minute or superficial lesions are found involving too much of the gastric wall to treat locally. Surgery is rarely advised until life is despaired of. As a result, the condition of many patients is so critical when medical treatment is abandoned that only the simplest type of operation can be considered. Finney[4] advised gastrotomy and thorough search for the source of bleeding. Walton[5]; occlusion of the pylorus and gastroenterostomy without search for the bleeding vessel. Cunéo[6]; gastrotomy and ligation, cauterization or electrocoagulation of the bleeding points, citing Cazin's twenty-five cases with twenty-three recoveries and Kraft's five cases with four recoveries. Sènèque[7] and Mallet-Guy and Peycelon[8]; ligation of "different pedicles" of the stomach when no ulcer is found. Tixier and Clavel[9] reported two recoveries of very critical cases after jejunostomy. Local treatment of the bleeding points or superficial ulcers, if present, is apparently of some benefit. When no lesion is found, ligation of gastric vessels or jejunostomy may be of value. On the whole, surgery, the last resort in these cases, saves but few.

A high percentage of all gastric hemorrhages are due to chronic ulcer. Miller[10] reviewed 151 cases at the Hospital of the University of Pennsylvania and found that 62 per cent were due to ulcer. Rivers[11] reported that 90 per cent of the cases of hematemesis at the Mayo Clinic were due to intragastric lesions. Statistics from many writers are irrelevant as gastric and duodenal

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hemorrhages are not differentiated. Bleeding occurs in about 25 per cent of chronic ulcers. Balfour[12], Truesdale[13] and Bock[14] have reported cases of diaphragmatic hernia resulting in gastric ulcer with hemorrhage. A small number of gastric hemorrhages are due to malignancy. Balfour reported 7.5 per cent, Miller 22 per cent and Finsterer[15] 3 per cent.

Symptoms of acute bleeding from a chronic ulcer do not differ from acute gastric hemorrhage from other causes except in rupture of large vessels as the coronary, splenic, etc. In these cases the blood loss is extremely rapid and often fatal. Conservative treatment is of little benefit and the only hope lies in early operation.

A high percentage of bleeding chronic ulcers are controlled by conservative treatment. A small number recover completely. Persistent ulcer symptoms after cessation of a hemorrhage require surgical treatment, but operation should be withheld until considerable improvement is noted in the patient's condition, preferably a few months.

Hinton[16] reported a mortality of 11 per cent in 80 cases of severe gastric and duodenal hemorrhage treated medically, Chiesman[17] 25 per cent in 191 cases, Ross[18] 58 per cent in 45 cases and Lynch[19] 12.9 per cent in 31 cases. The number of gastric ulcers in these reports is not stated. Finney gives the mortality from bleeding ulcer as 29.5 per cent. It is evident that there is an opportunity for considerable improvement in the medical management of these cases.

Continued or repeated bleeding from a gastric ulcer under medical treatment is an indication for surgical intervention. How many attacks of bleeding and how long the bleeding shall be allowed to continue are matters of individual judgment. An estimate of the amount of blood lost in the vomitus and stools may be very misleading. The red cell count is a more accurate index of the patient's condition. A steady fall in the red cells to below two million with repeated or continued hemorrhage is an indication for immediate surgical intervention. If medical treatment has been prolonged with repeated transfusions the surgical risk is increased as the mortality increases with each hemorrhage and the benefit from transfusion decreases.

Balfour advises operation if a second hemorrhage occurs before the patient has recovered from the initial attack. Choyce[20] recommends operation in all cases of chronic ulcer. "as soon after the cessation of the first bleeding as their condition will permit". In cases of continued bleeding after absolute rest he advises immediate operation. Finsterer reported 42 cases operated after the initial acute hemorrhage with a mortality of 4.8 per cent and cited Friedman's report of 1927 consisting of 18 early operations with one death. The severity of the hemorrhage in Finsterer's cases may be questioned as he mentioned the use of transfusion in few patients. His operative procedure in most cases was ligation of the bleeding vessel or excision of the ulcer.

Hypnotics, external heat and other means to combat shock are advised preoperatively in all cases. The benefit derived from saline, glucose and transfusion will depend upon the patient's condition and the duration and amount of preceding medical treatment.

The first attempt to treat massive gastric hemorrhage surgically was by von Eiselberg[21] in 1880. A resection with the thermocautery of an ulcer on the lesser curvature was done with a fatal result. The first successful operation was by van Kleef[21] in 1882. Roux and Mikulicz[22] in 1897 reported one successful case and three fatalities following operation for acute hemorrhage. Mayo-Robson[21] reported 69 per cent mortality in 1900 following surgical treatment of 12 cases, Hartmann[21] 62 per cent mortality in 1903 and Tuffier[21] 37 per cent mortality in 42 cases in 1905. Little improvement in surgical treatment has been made in recent years.

Any surgical treatment should be the simplest possible to obtain hemostasis (Pfeiffer[23]). In the non-adherent chronic ulcer, mass suture, cautery puncture and infolding the ulcer or ligation of tributary vessels in large ulcers are effective and productive of little shock. Adherent ulcers are a more difficult problem, often requiring separation of adhesions and excision or mass suture of the ulcer with ligation of bleeding vessels in the pancreas. A less difficult approach in some instances is through a gastrotomy incision. Radical methods are indicated in the less severe cases as excision of the ulcer with gastroenterostomy or the various types of resections.

The following series of 116 cases has been seen in my private practice.

Duodenal Ulcer	93	Perforated	25	Hemorrhage	9	Massive	5	Death	5
Gastric Ulcer	23	Perforating	3	Hemorrhage	10	Massive	4	Death	1

The cases of duodenal ulcer are included to show the relative frequency of the two lesions: about four duodenal to one gastric. Hemorrhage occurred in a higher percentage of cases in gastric ulcers than in duodenal, ten gastric to nine duodenal. There were five cases of massive duodenal hemorrhage, all of which were treated conservatively and died. Four patients with gastric ulcer had massive bleeding, two were treated conservatively with one death and two operated upon successfully.

CASE 1: November 10, 1925, E. S., male, aged fifty. Always well except for attacks of "biliousness and sour stomach" for many years. Yesterday afternoon

while at work, he suddenly vomited a large amount of blood and fainted. He was carried home, put to bed and given morphine and a hypodermoclysis. This morning he vomited about one and a half quarts of dark blood. He was seen at his home with Dr. Baker of Middleboro in the late afternoon. He was pale, blood pressure 40, hemoglobin 30 per cent. Abdomen moderately distended. A transfusion of 500 cc. was done at once. The following afternoon he vomited about one pint of bright blood and the next morning, November 12, vomited fully a quart of blood. His condition was extremely grave when he was seen at 6 P.M., semi-conscious with imperceptible pulse and blood pressure. A second transfusion of 500 cc. was done. The following day his condition was greatly improved, but in the afternoon he vomited a pint of blood. A third transfusion of 500 cc. was given. He had no more bleeding after this transfusion and made an uninterrupted recovery with no recurrence to date. X-rays one year after the hemorrhage showed an irregularity of the lesser curvature suggestive of healed ulcer.

CASE 2: January 24, 1929, W. C., male, aged seventy-four. Referred by Dr. Record of Abington. Had many attacks of severe epigastric pain with slight hematemesis and dark stools for five years. Attacks preceded by heavy drinking. For the past two days he has vomited bright blood frequently "about a cupful at a time" and has passed many tarry stools. He was semiconscious on admission, extremely pale, pulse rapid and thready, with imperceptible blood pressure. Red count 1,500,000; hemoglobin 25 per cent. He was given shock treatment and preparations were made for transfusion but he died before any blood was given him.

CASE 3: January 1, 1921, W. P., aged thirty-eight. Referred by Dr. Baker of Middleboro, Mass. History of ten years' "stomach trouble" which necessitated giving up work for the past two months. Operation: cautery puncture and infolding duodenal ulcer, posterior gastroenterostomy. Relieved for five years, then in 1926 had recurrence of symptoms. X-rays at that time showed a perforating ulcer of the lesser curvature of the stomach. Not heard from until May 2, 1931 when he was admitted to the Moore Hospital with the following history: his stomach symptoms have gradually increased in the past six years in spite of treatment. During the past six days has passed four dark, bloody stools and last night vomited a large amount of blood and again at 4 A.M. and 12 noon to-day. He was moderately pale. Systolic pressure 80, hemoglobin 50, red count 2,500,000. A transfusion was done of 500 cc. May 6, he said he felt very weak and passed two large dark movements. May 9, he seemed worse and passed more dark stools. A second transfusion of 500 cc. was given. May 10, he vomited over a quart of bright blood. A transfusion was done at once. Immediately after, he was operated upon under ether. A large bleeding ulcer was found on the lesser curvature which was cauterized (puncture) and infolded with mass sutures. He had no further bleeding and made a slow but satisfactory recovery. He has been quite free from stomach symptoms since 1931 until a few weeks ago. Since then he has had a recurrence of epigastric pain and indigestion.

CASE 4: May 31, 1932. F. C., female, aged fifty-nine. Referred by Dr. Elliott of Middleboro, Mass. Had indigestion and occasional attacks of vomiting for past fifteen years. Has noticed dark colored movements the past four weeks and has lost strength and color rapidly. Eight days ago vomited twice, very dark vomitus. She was extremely pale and very weak. Hemoglobin 30 per cent, red count 2,000,000, moderate epigastric tenderness. X-rays of the stomach showed a probable gastric polyp. June 4, transfusion of 500 cc. She passed several tarry stools and on June 13, her hemoglobin was 40 per cent and red count 1,500,000. June 14, she was given 500 cc. of blood. June 15, operation under avertin and ether. An indurated ulcer 3½ cm. was found in the posterior wall of the stomach adherent to the pancreas. A 3½ inch incision was made in the anterior wall of the stomach, the ulcer was separated from the pancreas and excised. The opening in the posterior wall of the stomach was closed transversely. Convalescence was uneventful and she has remained well since.

CONCLUSIONS

The mortality of gastric and duodenal hemorrhage from all causes is said to be from 3 to 5 per cent. Statistics of gastric hemorrhage alone are not available in the literature.

I have emphasized the importance of recurrent and continued massive hemorrhage, as the mortality under medical treatment is reported as high as 58 per cent and of the patients operated upon much higher.

Massive gastric hemorrhage occurs in a small number of patients without an ulcer history and without visible evidence of a ruptured vessel. Surgery is not advised in these cases while expectant methods offer any hope, as the operative mortality is discouraging.

A high percentage of gastric hemorrhages, however, are due to chronic ulcer. It would appear that earlier operation in these cases might result in a lower mortality.

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DISCUSSION

DR. WALTER C. SEELYE, Worcester, Mass.: *Mr. President and Gentlemen of the Society*—Dr. Moore has brought his subject before you in a complete and interesting manner, and has covered the ground so well that it leaves very little to discuss.

I want to reiterate his point that apparently he is dealing with gastric bleeding ulcers and not duodenal bleeding ulcers. As Morgan has pointed out, the massive gastric bleeding ulcers usually occur from small and acute ulcers, and these acute ulcers are usually multiple, as has been demonstrated in autopsy, even only a millimeter or two in diameter.

These ulcers are found to have a ruptured artery at the base, and being almost always multiple, could with great difficulty be found in a trans-gastric operation.

Chronic ulcers may also bleed, to any degree, from slight to massive hemorrhages. Chronic ulcers obtain fibroses, and those on the lesser curvature show that the large arteries of the stomach at some distance from the ulcer are drawn into the base of the ulcer by massive fibrosis, and it is in that type of chronic ulcer that we get the bleeding of any considerable amount. When dealing with massive hemorrhage of the stomach, we are faced with a condition requiring utmost judgment in regard to treatment which may be medical or surgical according to the situation at hand.

Medical treatment, Dr. Moore has shown you very clearly, and when that fails, there are cases that have to be operated upon which, if found to be the type of chronic ulcer, with induration, offer much more likelihood of controlling the hemorrhage than small multiple, acute ulcers which so often occur.

In the latter they cannot be observed from the examination of the outside of the stomach, and I feel that it is futile to open the stomach in any attempt to find a bleeding point, but the chronic ulcer, with induration, can always be found by examination of the stomach, and cautery puncture by the Balfour method does lend a very important means of controlling the hemorrhage, for in all probability that ulcer alone is the seat of the hemorrhage.

In cases of bleeding from multiple, small, acute ulcers, if desperate, and medical treatment fails, I feel that the only possibility of cure is a quick gastroenterostomy. That is the operation of choice rather than trying to find the bleeding point by opening the stomach.

DR. ARTHUR W. ALLEN, Boston, Mass.: Some of you will remember that I reported before this Society two years ago a group of duodenal ulcers with massive bleeding. We found that about one third of duodenal ulcers bleed, and that 0.3 per cent of all bleeding duodenal ulcers died of hemorrhage; and that 14.5 per cent of those who bled massively died of hemorrhage. Also, that in this group, most of the deaths occurred in patients over fifty years of age.

We have recently studied the gastric ulcer records in relation to bleeding and mortality for a ten-year period. Four hundred and thirty-four gastric ulcers were treated as hospital patients during this time. One hundred and twelve of these cases bled. Six died of hemorrhage, or 5.3 per cent of the bleeding gastric ulcer cases bled fatally.

In going over these records, we chanced across two cases of cancer of the stomach, one of gastritis, one gastric polyp and a gastrojejunal ulcer ending fatally from hemorrhage.

Most of us, I believe, agree that operation during the acute stage of hemorrhage is a serious undertaking. I feel, however, that in massive hemorrhage from duodenal ulcer in patients near middle life, we must be prepared to do radical surgery in the acute stage if there is indication that spontaneous cessation is unlikely. A method of attack was described by Dr. Benedict and me in the Annals of Surgery, October, 1933. I wish to reiterate here that this should be done only on rare occasions and in properly selected cases.

I wish to congratulate Dr. Moore on his presentation and commend him for his willingness to attack massive gastric hemorrhage early in proper cases. I do not believe that the age question is so relevant in the gastric ulcer as in the duodenal, but am not prepared to make a definite statement concerning this to-day. I am impressed by the fact that we should be radical in gastric ulcer bleeding more often than in duodenal.

We should not wait until these patients are *in extremis* before resorting to surgery. Many of them will live several days and die of a final hemorrhage, even after repeated transfusions. They are depleted from starvation as well as blood loss and are easy subjects for pulmonary complications and infection. We must select the cases for radical surgery in the first forty-eight hours. If a patient bleeds out one transfusion carefully and slowly given, he should be taken to the operating room, given a massive transfusion or two and radically operated upon.

In the gastric ulcer group, I advocate opening the stomach as Dr. Moore has demonstrated, evacuating the clots and treating the ulcer from within. The actual bleeding vessel can be seen from within and then ligated on the outer side of the stomach in most cases. A gastroenterostomy as Dr. Seelye has suggested, should be added if the patient's condition permits. I wish to warn against simple gastroenterostomy in massive hemorrhage either from gastric or duodenal ulcer. If these patients are the type that should have emergency surgery, they will continue to bleed after simple gastroenterostomy.

DR. GEORGE A. MOORE, Brockton, Mass.: The type of operation would appear to deserve emphasis in these cases of massive gastric hemorrhage, as they are extremely grave surgical risks. The operation should be planned to fit the individual case. Some temporary method of hemostasis, as mass suture of the ulcer or ligation of tributary vessels, is as extensive an operation as their condition will permit. Excision of the ulcer, or gastroenterostomy, should be withheld until the patient recovers from the hemorrhage.

TYPICAL EPILEPTIC SEIZURES IN THE COURSE OF SCHIZOPHRENIA*

A Report of Two Cases

BY EDWARD F. FALSEY, B.S.†

SINCE the appearance of Notkin's review[1] in 1929, in which he presented five cases, there have been a few scattered reports of patients in which various admixtures of epileptic and schizophrenic syndromes have been described. The rarity of such combinations has been constantly emphasized, and in the majority of the cases reported, the epileptic attacks either preceded or initiated the psychosis diagnosed as schizophrenia. Thus in Notkin's five cases, the first had epileptic seizures prior to the development of his psychosis; the second presented a history of convulsions in childhood; the third had a series of fainting attacks, probably petit mal in character, which were not complicated by the schizophrenic picture until the patient was thirty-seven years of age. In the fourth case, however, an epileptic convulsion appeared eight years after admission to the hospital at the height of the psychosis, schizophrenia of the paranoid type. There is in Notkin's fifth case a definite history of head trauma in childhood, and when the two convulsions occurred in this patient, he presented the clinical picture of manic-depressive psychosis, manic phase, rather than of schizophrenia.

In the case of R. K., reported by Krapf[2], in 1928, the convulsion described is probably correctly attributed to the hyperventilation which occurred during the catatonic state, and is thus to be considered tetanic rather than epileptic in character.

Rosental[3], in 1920, stated that he had never seen a classical epileptic attack in catatonia and had found no description of one in the preceding literature.

Gruhle[4], in a review in 1924, said that he had never seen a fully developed motor attack of the major type in schizophrenia. Penacchi, from the Psychiatric Hospital in Perugia, reported three cases in which epilepsy and schizophrenia were associated and stated that in the instances in which the epileptic attacks precede the schizophrenic picture, the latter may properly be regarded as an epileptic psychosis, although it may closely simulate schizophrenia. The other cases in which schizophrenia precedes the epileptic attacks he considers extremely rare. He expresses the belief that in either instance one must look for a "peculiar constitutional condition of the subcortical as well as cortical centers".

Glaus[6] presented eight cases in which a double diagnosis of schizophrenia and epilepsy was made, but pointed out that in four of these a purely successive combination was involved in which epileptic attacks had made their appearance many years before the onset of the psychosis. Even in the acute catatonic exacerbations of the later schizophrenia, there resulted in his cases no tendency to produce further attacks. Of his other four cases in which schizophrenia and epilepsy occurred together, there was but one in which he believed a causal relation existed between the catatonic state and an epileptic seizure. He concluded that schizophrenia has on the whole really unimportant pathogenic significance in the release of epileptic attacks or in the production of epileptic equivalents. The epileptiform attacks in the course of catatonia, occasionally observed, Glaus regarded as catatonic symptoms or as exogenous reaction forms which are simply symptomatic and have nothing to do with epilepsy in the narrower sense. He stresses the fact that in none of the schizophrenia-epilepsy syndromes can an epileptic family background be demonstrated.

The two cases presented herein are both instances of young individuals in which arteriosclerotic and luetic factors may be definitely ruled out as possible etiological factors in the pathogenesis of the seizures. In each instance, the seizures described were typically epileptic and occurred for the first time during a catatonic exacerbation of a rather long-standing schizophrenia. In neither instance have the seizures recurred since the acute catatonic phase of the psychosis has subsided. In one case there was a mild infection (nasopharyngitis) and a mild elevation of non-protein nitrogen (44.4 mgm./100 cc.) during the period of epileptic manifestations. It would appear in the following that the epileptic seizures described were either released by the catatonic episodes, or were the result of the same etiological factors involved in the exacerbation of the psychosis. Thus they appear to be a reflection of deep-seated vegetative, metabolic, or psychobiological changes which not only were concomitant with the psychosis, but which so lowered the convulsive threshold that epilepsy appeared.

CASE 1. (R. I. State Hospital for Mental Diseases No. 18,400.)

J. B., a single white woman of Scottish descent, twenty-four years of age, was transferred to the State Hospital from the Charles V. Chapin Hospital

*From the State Hospital for Mental Diseases, Howard, R. I.
Acknowledgment is made to the staff of the State Hospital, especially to Doctors Noyes, Kasanin, Ping, and Sumberg, from whose progress notes and impressions the writer draws freely in the description of the clinical course and diagnoses of the cases presented.

†Falsey, Edward F.—Junior Interne, Rhode Island State Hospital for Mental Diseases. June-September, 1934. For record and address of author see "This Week's Issue," page 168.

on July 24, 1934 because she had been acting peculiarly and had been noisy "and assaultive." Her family history was negative for outspoken nervous and mental disease. The patient's father was a stern, harsh man; her mother a nervous, nagging woman, who kept the family under control by continual complaining and weeping. At the onset of the patient's present illness, the family group consisted of her father, mother, and one brother, twenty-two years of age.

The patient was born in a village in Scotland on September 29, 1909. Birth and early development were normal. The patient was described by her brother as a "perfect child", who never got into difficulty at home or at school. The patient came to this country at thirteen years of age and attended high school for two years. She was a good scholar but was required to leave school at the end of that time to assist her mother with the housework. She secured an occasional odd job and attended night school where she finished a commercial course. After graduating she obtained employment as clerk in a bank and was fairly successful, her earnings rising to $21.00 per week after three years there. The patient had always been healthy and had had no operations, accidents, or serious illnesses until the onset of the conditions for which she was admitted. Careful questioning of two informants (patient's mother and brother), revealed no history of head trauma and at no time did the patient exhibit convulsive phenomena in childhood. Menstruation began at fourteen and was regular. The patient did not use alcohol or tobacco. She was considered a good-natured girl and was rather athletically inclined. She was active in church work and liked to dance. All her earnings were turned over to her mother who purchased the patient's clothes, which were old-fashioned and which made the patient feel conspicuous in her social group. The patient's mother was extremely domineering and seldom permitted her to leave the home in her search for amusement.

The patient's mental illness began early in January, 1931, when for a week she complained of feeling blue and depressed. She was unable to work and sat staring into space, occasionally expressing the belief that people were against her and that they were calling her a "bad girl". She was admitted to the Charles V. Chapin Hospital and transferred from there to Butler Hospital on February 14, 1931. She expressed delusions of persecution, was suspicious and evasive and at one time attempted suicide. On March 14, 1931, the patient became very active, screaming wildly and tearing madly about the ward. She was resistive and had to be spoon-fed, but grew quieter during the following two months and was able to leave the hospital on July 31, 1931. Diagnosis on discharge from Butler was manic-depressive psychosis, manic phase.

Following her discharge from the hospital the patient was subjected to even closer parental supervision. Until June of this year, the patient was submissive and made only occasional attempts to find employment. For a week she worked as substitute clerk in a hat shop and two or three months in the summer of 1932 she was a clerk in a drug store. During the spring of 1934 she took up gardening as a hobby.

Early in June, 1934, the patient became anxious to obtain work and finally located a position as waitress at a sea-shore resort which necessitated her living away from home. Her mother was very actively opposed to this move and wept copiously, but the patient finally broke with her and left her home. Five days after beginning work, the girl's actions became manifestly abnormal. She rose at 4 o'clock in the morning and went into the fields to pick flowers. Her conversation became rambling and disconnected and she grew noisy and assaultive when she was brought home. On June 20, 1934 she was admitted to Charles V. Chapin Hospital where she was hyperactive and resistive, was obviously hallucinated and had to be tube-fed. In two weeks there, she became denudative and incontinent and at times would stretch herself on the floor in the attitude of the crucifixion. Diagnosis of schizophrenia was established and the patient transferred to the State Hospital for Mental Diseases at Howard, R. I., on July 24, 1934.

During the first few days in the State Hospital the patient was quite retarded and displayed hesitancy, bewilderment, withdrawal, and preoccupation. She had during the first three days of her residence three seizures which were typically epileptic in character. Each lasted three to five minutes and was first manifested by the patient losing consciousness and falling to the floor. Each time the musculature of her extremities went first into tonic spasm and then exhibited the typical clonic contractions. The muscles of mastication were likewise involved in these contractions and she lacerated her tongue severely. Her eyes were rolled upward during the seizures and flecks of foam appeared on her lips. The patient fell asleep after each seizure and her consciousness was clouded for several hours. Luminal was started immediately and she was free of convulsions by July 27. On that day she became extremely disturbed, moving restlessly about, singing and slapping herself. She grew quiet after being placed in continuous baths for a brief period, and since then her clinical picture has been characterized by her assumption of numerous unusual postures and by various contortions of her body. At times she has been flaccid, limp, and almost lifeless in appearance. She has not had any seizures since July 27, although luminal was discontinued on August 17.

At psychiatric examination on July 27 the patient was disoriented for time and place, but her answers to questions were coherent and relevant at that time. She was, however, quite preoccupied and her apperceptive powers were impaired by the concentration of her mental effort on the subject of her orientation. She denied auditory and visual hallucination, but exhibited an incomplete amnesia for the events which preceded her admission to the hospital. She made no attempt at confabulation and seemed somewhat dazed. Her judgment was very poor, but she showed partial insight by recognizing that she was in an abnormal mental state. Physical examinations on July 24 and 25 were negative. Laboratory examinations were negative except for a leucocytosis of 18,400 on July 25, which by August 2 had fallen to 8,200.

At a staff conference on August 17, the patient's emotional reactions were quite inadequate and rigid, and it was frequently not possible to secure any answer to questions directed to her. Diagnosis of schizophrenia was made and her general reaction was considered by Dr. Noyes to be "certainly not dissimilar to a catatonic excitement". The convulsions described above were considered incidental phenomena in the general vegetative and metabolic derangement accompanying her acute and deep-seated psychosis.

CASE 2. (R. I. State Hospital for Mental Diseases No. 18,444.)

F. G., a twenty-one year old married Italian woman, was first admitted to the R. I. State Hospital for Mental Diseases on August 28, 1931, being transferred from Providence City Hospital where she had been negativistic, mute, and untidy, and where she had to be tube-fed.

The patient had one brother admitted to the State

Hospital in 1925, whose condition was diagnosed as schizophrenia; otherwise there was no history of nervous or mental disease, or of alcoholism. The patient was born June 20, 1913, was the youngest of three siblings, and as a child was considered "stubborn". She started school at eight years of age and completed the eighth grade at fifteen. She then assisted in the housework at her home. She was quiet and apparently happy although very self-contained. She had always been quite religious.

Her sister had noted an increasing instability and nervousness in the patient beginning in 1929. In July of 1931, an appendectomy was performed on the patient, and following her discharge from the hospital, she had become depressed and refused to eat or talk at home. She had accordingly been admitted to the Providence City Hospital where her condition was as described above and where the diagnosis of dementia praecox, catatonic form, had been established. Under hydro- and occupational therapy, the patient's condition gradually improved after her transfer to the State Hospital, and she was paroled in November of 1931. She had considerable difficulty in making adjustment outside the hospital. In March, 1932 she contracted a Neisserian infection. The patient was returned on three occasions until finally paroled, against advice, in May, 1933. After that date she obtained work and became engaged to be married. The patient then exhibited no abnormalities of behavior until the day before her wedding. On June 25, 1934, she cried most of the day. She insisted at the last moment that she be married with a high mass, although other arrangements had already been completed. On the morning of her wedding she complained of a sore throat. Sexual adjustment was satisfactory but on the night of June 28 she screamed and told her husband that her brother was observing them through the door. Two days after this episode she appeared to be unable to arrange dishes properly on the table. She talked incoherently about her father and mother and about a brother who had died when she was five years old. The following day, while she was accompanying a friend on a city street, a clock struck the noon-hour and the patient knelt suddenly and began to pray loudly, crossing herself and calling upon the saints. She was brought to Providence and admitted to the Charles V. Chapin Hospital on July 11. There she was elated, restless, and uncoöperative and before her transfer became denudative and incontinent. It was necessary to tube-feed her until her entrance into the State Hospital on August 23, 1934.

During that day she remained mute but was fairly coöperative to physical examination. On August 24 she had the first of a series of typical epileptic seizures. On the twenty-fifth she was observed in two of these, each lasting approximately three minutes, and spaced at intervals of three minutes. In the first, she bit her tongue rather severely and the musculature of her extremities went first into a tonic state and then into clonus. On the twenty-sixth she had six seizures, each one being followed by a clouded state. In spite of anti-convulsive treatment, her seizures of the grand mal type continued to occur frequently until August 29 when their character apparently changed to a petit mal type. She had, for the following four days, numerous attacks of the petit mal character, but since September 2, 1934 has been totally free of seizures. During psychiatric examination on September 4, 1934 the patient's predominant attitude was one of apathy and she was obviously disinterested in the interview. She was preoccupied and at times hallucinated in the visual field. Her orientation for place was accurate and her powers of apperception not fundamentally impaired. Her emotional reactions were superficial and her emotional responsiveness inadequate. There was obvious scattering and at some points, blocking in her stream of thought. Her ideational content was characterized by a considerable burden of guilt. She had apparently regressed considerably and her judgment was extremely poor. She had no insight into her condition.

Physical examination on August 23 revealed the following positive findings: (1) nasopharyngitis, (2) hyperactive deep tendon reflexes and (3) B.P. 142/90, leucocyte count on August 23 was 11,550; on the twenty-eighth it was 10,200. Wassermann and Kahn were negative. N. P. N. on August 27 was 44.4 mgm. per 100 cc; on September 7 N. P. N. was 24.3 mgm. per 100 cc. X-ray of the skull was negative.

Neurological examination on August 29 revealed bilateral equivocal Babinski reactions and questionable ankle clonus. On September 9, Babinski response was flexor and ankle clonus definitely absent. Diagnosis established at staff conference on September 10, 1934 was schizophrenia with epilepsy.

SUMMARY

1. The rarity of typical epileptic seizures in schizophrenia is constantly emphasized in the literature.

2. Two cases are presented in which young schizophrenic individuals at the height of a catatonic exacerbation of their psychosis exhibited, for the first time, typical epileptic seizures of the grand mal type.

3. The etiology of these attacks is attributed to profound vegetative, metabolic, or psychobiological changes concomitant with the catatonic states.

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PRIMARY CARCINOMA OF THE VAGINA*

BY JOHN T. WILLIAMS, M.D.†

PRIMARY carcinoma of the vagina is extremely rare. Ewing[1] quotes Schwartz that it constitutes 0.24 per cent of all carcinomata, and Williams to the effect that only 0.43 per cent of all cancers in women have their origin in the vagina. Primary carcinoma of the vagina must not be confused with secondary carcinoma, the result of extension from the cervix, which is extremely common, or the occasional implantation metastases from an adenocarcinoma of the corpus uteri.

The percentages quoted by Ewing, small as they are, seem to me to be unduly high, for in a search of the records of the Pathological Department of the Boston City Hospital, I could find only two undoubted specimens of primary carcinoma of the vagina recorded during a period of twenty-five years, 1906 to 1930 inclusive. One of these was my own personal case to be described in some detail.

Moench[2] of the Mayo Clinic has analyzed fifty-nine cases observed between the years 1904 and 1930. Her paper includes cases previously reported by Broders[3] and Stacy[4]. According to Moench the relation of primary cervical to primary vaginal carcinoma is forty-three to one, which certainly overstates the frequency of primary carcinoma of the vagina in common experience.

Graves[5], Anspach[6], Lynch[7], and others in textbooks mention the existence of primary carcinoma of the vagina, but do not cite cases. Bailey and Bagg[8], Tuft[9], Holland[10], Singer[12] and Moench[2] have reported cases in more or less detail.

Healy[11] in a recent paper reports *en bloc* ninety-nine cases of vaginal carcinoma. It seems improbable that these could have been all primary in the vagina, even in a clinic the size of that at the Memorial Hospital.

Histologically all primary carcinomata of the vagina are epidermoid in type and derived from the squamous epithelium of the vagina. Although Broders[3] believes that adenocarcinoma may develop from the basal layer of the pavement-epithelium, the occasional reports of adenocarcinoma of the vagina should be looked on with suspicion as probable implantation metastases from a growth primary in the corpus.

The most common location is on the posterior vaginal wall (Lynch[7], Graves[5], Moench[2]). Practically all writers agree that irritation from a pessary is not a predisposing factor. Previous childbearing is also of doubtful etiological significance. The Mayo series[3], which is the only detailed one on record, showed in an analysis of forty-one patients with primary carcinoma of the vagina, thirty-six married and five single women, and of the married women 17 per cent had not borne children, which after some mathematical computation, makes the proportion of presumable nulliparae about 27 per cent.

The symptoms are identical with those of cancer of the cervix; thin watery discharge becoming blood-stained, with intermittent periods of free bleeding. The diagnosis is easily made on vaginal palpation and inspection, but should be confirmed by biopsy.

The following cases are reported in some detail as the only two undoubted instances of primary vaginal carcinoma admitted to a busy gynecological service in a period of twenty-five years.

CASE 1. Miss S. M., aged fifty, single, a cook by occupation, was admitted to the Boston City Hospital Jan. 26, 1915, with the following history: The menopause had occurred without incident sixteen years before. For some months she had suffered from a foul, yellow vaginal discharge, but had not sought treatment until she developed a severe dysuria.

General examination showed a senile appearing cachectic woman. No marked pathology in the chest or abdomen was found. Local examination revealed a firm, ulcerated mass involving the anterior vaginal wall just above the introitus and obviously infiltrating also the bladder wall. Biopsy showed epidermoid carcinoma originating in the vaginal epithelium. The cervix was intact and the uterus of small size.

This case was inoperable and was simply given terminal care, dying from cachexia five weeks after admission.

CASE 2. Mrs. H. W., aged seventy-two, a widow, no occupation, was admitted to the Boston City Hospital May 7, 1930. Her past history was as follows: She had had four normal labors and no miscarriages, an appendectomy in 1899, but no other important illnesses. The menopause had occurred in 1908 without incident. Five weeks before admission she had had a slight staining and three weeks later a profuse vaginal flow followed by more staining.

General examination showed an elderly woman apparently in fair condition, although a slight cardiac irregularity and a blood pressure of 180/120 were noted.

Local examination revealed a cauliflowerlike growth, 1 and ½ inches in diameter at its base, located one inch from the cervix and slightly to the left on the posterior vaginal wall. The cervix itself, although prolapsed to the introitus, was not ulcerated or eroded. There were moderate cystocele and rectocele.

It was decided to perform a biopsy and treat the growth with radium at the same sitting.

On May 8 an attempt was made to excise a portion of the neoplasm for microscopic examination, but owing to excessive bleeding it was necessary to remove the entire growth in order to control hemorrhage. Following excision 100 mgm. of radium bromide screened in 2 mm. brass and enclosed

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in rubber tubing was placed against the site of removal and left for twenty hours (2000 mgm. hours of radiation).

Dr. Mallory examined the specimen personally and reported epidermoid carcinoma. He also made a microphotograph of the growth, which I am able to reproduce with this article.

The patient had very little reaction, and the wound healed quickly. I have had the opportunity of following this patient to date. The vagina remained clear for nearly three years, when a slight recurrence was noted. On May 8, 1933, three years to a day from her operation and first radiation, she was again radiated, this time being given 2400 mgm. hours by the same technique.

The recurrence quickly disappeared and examination one year later (May 14, 1934), showed the vagina well cicatrized at the area of radiation. No ulceration, induration or infiltration could be found.

Treatment of primary carcinoma of the vagina should be by radiation. The accessibility of the growth and the probability of early extension to contiguous organs combine to make the application of radium the choice over any method of excision. The radium application should be followed by deep x-ray therapy at a later date.

The prognosis is poor, however, in the majority of cases. Bailey and Bagg[8] treated eighteen cases by a combination of needling and vaginal tubes held in place in dental compound. Only four patients were free from recurrence at the end of two years.

In Moench's series[2], of fifty-three cases in which the end-results were known, only 17 per cent could be considered as cured. Similarly Healy[11] reported only 12 per cent of five year cures.

These poor results are undoubtedly the result of early invasion of contiguous organs.

CONCLUSIONS

1. Primary carcinoma of the vagina is rare but easy of diagnosis.
2. The symptoms are identical with those of cancer of the cervix, the diagnosis resting on inspection and biopsy.
3. Because of easy accessibility the application of radium is simple.
4. Because of the early extension to contiguous organs and tissues, excision is contraindicated as the first choice as a method of treatment.
5. Radium treatment should be followed by high voltage x-ray exposures.
6. The prognosis is poor, about 25 per cent being free from recurrence at the end of two years, and only from 12 to 17 per cent at the end of five years.

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Since this article was submitted for publication, a third case of primary carcinoma of the vagina has been admitted to the Gynecological Ward of the Boston City Hospital. This patient entered on Oct. 24, 1934. She was sixty years of age, the menopause had occurred eleven years previously. For two months she had suffered from intermittent vaginal bleeding.

Examination showed a polypoid growth arising from the anterior vaginal wall, bleeding slightly on touch. On October 27 this growth was excised with a wide base. The pathologist reported it a slowly growing, well differentiated, epidermoid carcinoma. Following excision, 2500 mgm. hours treatment with radium element was given.

The patient left the hospital on November 3, with the site of excision well healed. It is, of course, too early to give a definite prognosis in this case.

VERMONT STATE MEDICAL SOCIETY

GENERAL CONSIDERATIONS AND PRINCIPLES OF EXCRETION UROGRAPHY*

BY M. SWICK, M.D.†

EXCRETORY urography is the roentgenologic visualization of the urinary tract by the intravenous, oral, subcutaneous or rectal administration of substances that are radiopaque. These should be non-toxic and excreted by the kidney in high concentration. The substances thus far proved successful are the various crystalline stably-bound organic iodides known as Iopax, Skiodan, Neoskiodan and finally, Hippuran. The lantern slides which are presented have been obtained for the greatest part with a compound known as Hippuran, introduced by the author in 1933. The latter medium in distinction to the others, is the iodine derivative of a compound normally excreted by the kidney and representative of a product of metabolism. Chemically, Hippuran is the sodium salt of ortho-iodohippuric acid. It is non-toxic and excreted unchanged. Satisfactory urograms have been obtained with Hippuran by the intravenous, subcutaneous and oral routes.

GENERAL CONSIDERATIONS: Excretory urography has proved itself an invaluable aid in urologic diagnosis. However, like every other method, it is not without its limitations. The early enthusiasm of some, that cystoscopy, ureteral catheterization and retrograde pyelography would become of minor importance has proved itself unfounded. These various procedures must supplement one another; and where doubt exists, cystoscopy and retrograde pyelography should be carried out. The direct visualization of the urinary bladder and catheterization of the ureters are still irreplaceable in the urologic armamentarium.

Since excretion urography depends for its success upon the functional activity of the kidney parenchyma, one should constantly be aware of the renal and extrarenal factors that determine the net result in that functional activity; for only in this manner can one properly interpret and evaluate the anatomic results obtained. The normally functioning kidney possesses the ability to excrete substances in high concentration in a given short period; this may be characterized as the "thrust-excretion ability of the normally functioning kidney", 70 to 80 per cent of Hippuran, for example, being excreted within the first two hours. It is upon this concentrating property of the kidney that the success of excretory urography depends. As a corollary, where this concentrating power is either impaired or absent, as in the poorly functioning kidney, the roentgenologic visualization is correspondingly poor or entirely absent. Broadly speaking then, it may be stated that the degree of visualization depends upon renal and extrarenal factors determining renal excretion.

FIGURE 1. Intravenous urogram—Right hydronephrosis due to aberrant vessel at the uretero-pelvic junction demonstrating the intense visualization that may be observed in cases of hydronephrosis and that therefore the intensity of roentgenologic shadow is not a quantitative measure of the healthy functioning renal tissue. The slight dilatation on the opposite side is indicative of a ureteral stone overlying the sacrum.

However, in the presence of urinary tract obstruction, visualization may still take place in those cases where the level of excretion normally required for roentgenologic purposes is impaired, provided that renal excretion still exists. Thus, in hydronephrosis, good visualization may still be encountered in spite of the existence of relatively little intact functioning renal tissue. An important concept to be derived from case illustrations bearing upon this consideration is the following, that in cases of hydronephrosis, the intensity of roentgenologic shadow cannot be relied upon as a quantitative measure of healthy functioning renal tissue or one for determining the type of therapeutic procedure. The latter will depend upon the individual case and upon the operative findings.

*Read at the Annual Meeting of the Vermont State Medical Society at Burlington, October 4-5, 1934.

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Again, the functional activity of the kidney may be temporarily diminished or perhaps totally inhibited as a result of either occluding lesions or trauma, although the kidney parenchyma itself be intact. The matter of total functional inhibition in the presence of intact renal tissue may be open to question and difficult of proof when considered in the light of experimental work. Yet for practical purposes, the concept of temporary functional inhibition may be permitted in cases where non-visualization of the urinary tract at one examination has been followed by the restoration of function with the removal of the causative factor. Such experiences have been observed in one case following trauma from retrograde pyelography and in another from a high occluding stone. Therefore, one should not always conclude that the kidney parenchyma is permanently damaged beyond repair because of the non-visualization at one examination.

In addition, instances of poor or no visualization, either bilateral or unilateral, in the presence of normal renal function as determined by excretion of indigo carmine, have been noted. These failures are difficult to explain. Perhaps, in some, the origin may be faulty technique. For one thing, I consider the application of compression by means of an air-inflated balloon over the urinary bladder region important in obtaining readable and suitably diagnostic urograms.

FIGURE 2. Intravenous urogram (with Hippuran). Diagnosis—Bilateral pyelonephritis.

FIELD OF APPLICATION: Case illustrations will demonstrate the field of application and usefulness of this method of investigation. Where retrograde pyelography has been contraindicated or difficult it has frequently shed invaluable light. For example, in the presence of hematuria, in obstructing lesions, in cases of implanted and reimplanted ureters, in congenital anomalies, in children and in individuals in whom instrumentation is harmful, excretion urography has been very helpful, aside from the fact that it offers in most cases a bilateral urogram. It is of very great help, particularly in patients presenting obscure abdominal symptoms and conditions, and in the differentiation of abdominal masses where one is adverse to subjecting the patient to retrograde pyelography. Chronic pyuria, usually attributed to simple pyelitis or pyelonephritis has been found to have its origin from congenital anomalies, infected hydronephroses, pyonephroses, tuberculosis, urinary calculus, or as in one case, urinary retention due to contracture at the neck of the bladder. Moreover, the mere non-visualization of a urinary tract as a result of disease of the renal parenchyma, as in pyonephrosis, is in itself of value in the localization and in the establishment of the diagnosis when viewed together with the other clinical data.

FIGURE 3. Same case as figure 2, by the subcutaneous method with Hippuran for comparison.

The contraindication to this method is uremia, for when the blood urea is high and the concentrating power of the kidney poor, the method yields few or no anatomic data and becomes not only superfluous but perhaps attended by danger.

Hippuran is manufactured by The Mallinckrodt Chemical Works, St. Louis, Mo.

MISCELLANY

NORTHEASTERN COUNTIES MEDICAL SOCIETY

The second quarterly meeting of the Northeastern Counties Medical Society was held November 24, 1934, in St. Johnsbury, Vermont. Twenty-four members enjoyed a delightful dinner served at the St. Johnsbury Hotel at 7 P.M.

The business meeting was called to order at 8 p.m. by President C. G. Schurman. The minutes of the last meeting were read by Secretary Edward A. Cramton, and accepted.

The name of Dr. Emily Taylor Wilson came up for election to the Society. She had been approved by the censors, Fitch, Leonard, and Piette, and was unanimously elected a member of the Society.

Secretary Cramton then introduced the guest speaker of the evening, Dr. Henry Jackson, Jr., of Boston, who spoke upon "Diseases of the Blood."

He said, in summary, the common blood diseases can be classified as follows:

1. Anemia due to lack of iron.
2. Anemia due to liver extract deficiency.
3. Anemia due to congenital hemolytic jaundice.
4. Leukemia, myelogenous and lymphatic.
5. Agranulocytosis.

Idiopathic hypochromic anemia is found most commonly in women of middle age. The red count may be nearly normal, the color index and hemoglobin very low. Hydrochloric acid is often absent from the stomach. Anemia due to hemorrhage, whether acute or prolonged, chlorosis and certain of the anemias of pregnancy are also microcytic anemias with a color index definitely less than 1. The treatment for all of these types of anemia is iron in large amounts. Feosol, grains XII a day, is probably the best and cheapest form of iron. If this is not available, Ferric Ammonium Citrate should be given in doses of four to six grams a day. It is seldom, if ever, necessary to use intramuscular iron.

To the second class of anemia, those due to liver extract deficiency, definitely belong pernicious anemia, pellagra and those due to marked pathological changes in the gastrointestinal tract. The anemia is macrocytic, the color index above normal. There is almost invariably an absence of hydrochloric acid in the stomach. Cord lesions are common and early and gastrointestinal disorders frequently precede the obvious anemia. The treatment for this class consists in giving sufficient potent liver extract. It may be given intramuscularly. Under these conditions the extract representing 100 grams of liver is given intramuscularly each week. This is probably the most inexpensive method of treatment. Liver may also be given by the oral route. Under these conditions one gives six vials of Lilly Extract No. 343 each day. Extralin may also be used. Failure of these patients to respond to adequate treatment is usually due to a wrong diagnosis, the presence of sepsis or the use of inert material.

Congenital hemolytic jaundice is best treated by splenectomy.

If an anemia will not respond to adequate liver or adequate iron therapy, it is probably irremediable.

The two types of leukemia are characterized by a great diversity of symptoms and a high and grossly abnormal white count. It is important to remember, however, that the diagnosis rests not so much upon the actual white count as upon the immaturity of the white cells. Both forms of leukemia respond to appropriate x-ray treatment, although it is questionable whether life is actually prolonged. The patient is made much more comfortable, however, by this treatment.

A large number of diseases, some of them not associated with the blood-forming organs themselves, give rise to moderate or extreme leukopenia. The disease, agranulocytosis, is probably a specific disease characterized by extreme leukopenia, absence of anemia, absence of hemorrhages and absence of thrombopenia. Certain of these cases are traceable to the administration of amidopyrine. In the majority, the etiology is unknown. At present, it is probable that the best treatment for this condition is the intramuscular injection of adequate (40 cc.) amounts of Pentnucleotide (N.N.R.). Even under the best of conditions, however, the disease remains a very fatal one.

RECENT DEATHS

DOANE — Isaac Randall Doane, M.D., of Springfield, Vermont, died in that city on July 13, 1934, after several years of ill health.

He was born in Bakersfield, Vermont, January 19, 1877, the son of J. Bradley and Ellen (Randall) Doane. He was educated at the Brigham Academy at Bakersfield, and the University of Vermont, receiving his degree in medicine from the College of Medicine of the University in 1904. He began practice in Springfield in association with his brother, the late Dr. C. Bradley Doane, and after a short time moved to Putney, Vermont, for two years. He then moved to Vergennes, Vermont, but after a few months returned to Springfield to assume his deceased brother's practice. During the next twenty-seven years, Dr. Doane lived in Springfield. He kept informed of the progress in medicine by attendance at the Mayo Clinic and by taking postgraduate courses in New York City. His devotion to his profession, together with his efficiency, led to the building of a large practice which prevented many other activities.

Dr. Doane was a member of the St. John's Masonic Lodge and Sigma Mu, national medical fraternity, and the staff of the Springfield Hospital.

He married Lucy Whitney in 1905. Of this union there are two children, Dr. Whitney R. Doane, who was associated with his father in practice, and Miss Shirley Doane, who is now in a school for hospital technicians in Worcester, Massachusetts. Besides his widow and children he is survived by a brother, Harry Doane, of Fairfield, Vermont, and a sister, Mrs. Celia E. Bennett, of Worcester, Massachusetts.

WARD—Henry S. Ward, M.D., of Springfield, Vermont, died at a sanatorium in Burlington, September 13, 1934, after an extended illness.

He was born in Guilford, Vermont, February 18,

1865, the son of Frank E., and Olive (Fowler) Ward. His early education was obtained in the schools of his native town and Brattleboro, and he graduated from the University of Vermont College of Medicine in 1887. His practice began in Readsboro, Vermont, and after several years he moved to Springfield, Vermont, where he acquired a large clientele. His interest in his profession was shown by several post-graduate courses at medical centers in New York.

He was a member of the Vermont State Medical Society, the American Medical Association, Windsor County Medical Society, and the Springfield Clinical Society. He was especially active in social and civic affairs, having served one term in the Legislature, representing the town of Readsboro, and two terms while living in Springfield, and was accorded important positions on committees of this body. He was a Mason, an Odd Fellow, a member of the Modern Woodmen of America, and the Congregational Church.

Dr. Ward was twice married, first to Mattie L. Carpenter of Readsboro, September 12, 1886. She died a few years later, and on April 15, 1897, he married Effie Carpenter of Readsboro. He is survived by his widow; one daughter, Mrs. Park H. Herrick, whose husband is Lieutenant in the 7th Field Artillery, U. S. Army, Fort Collins, Colorado; a sister, Mrs. Marion Wheeler, of Halifax, Vermont; a brother, Charles A. Ward, of Greenfield, Massachusetts; and two grandchildren.

COMPARISON OF DISEASE INCIDENCE IN CONNECTICUT WITH 1933 AND 1934 AND SEVEN YEAR AVERAGE

MONTH ENDING JANUARY 5, 1935

	1934					1933			
Diseases	Week ending Dec. 15, 1934	Week ending Dec. 22, 1934	Week ending Dec. 31, 1934	Week ending Jan. 5, 1935	Average cases reported for week corresponding to Jan. 5 for past seven years	Week ending Dec. 16, 1933	Week ending Dec. 23, 1933	Week ending Dec. 30, 1933	Week ending Jan. 6, 1934
Actinomycosis	—	—	—	1	—	—	—	—	—
Cerebrospinal Men.	1	—	—	1	—	—	3	—	—
Chicken Pox	216	183	122	149	134	155	103	84	160
Conjunctivitis Inf.	—	—	—	—	2	—	1	—	11
Diphtheria	1	2	1	4	16	10	2	7	2
Dysentery Bacillary	1	—	—	3	—	—	—	—	—
Encephalitis Epid.	—	—	1	—	—	1	—	—	—
German Measles	5	5	2	8	8	2	1	—	1
Influenza	6	8	81	236	131	4	5	23	13
Measles	314	316	278	433	129	17	5	3	21
Mumps	41	33	29	32	61	104	45	41	116
Pneumonia (Broncho)	22	20	36	33	41	44	39	35	53
Pneumonia (Lobar)	21	33	41	63	55	62	51	50	64
Poliomyelitis	—	—	—	1	—	—	—	—	—
Scarlet Fever	39	39	46	51	71	55	50	48	63
Septic Sore Throat	2	5	4	3	2	4	3	2	1
Smallpox	—	—	—	—	4	—	—	—	—
Tetanus	—	—	1	—	—	—	—	—	—
Trichinosis	—	2	—	—	—	—	1	—	—
Tuberculosis (Pul.)	25	15	17	13	28	21	25	8	13
Tuberculosis (O. F.)	2	—	3	—	2	—	2	4	1
Typhoid Fever	1	—	1	1	—	—	—	1	—
Undulant Fever	—	—	1	—	—	1	—	—	—
Whooping Cough	65	72	45	73	52	45	44	26	35
Gonorrhea	45	18	31	31	26	64	26	14	21
Syphilis	45	44	33	55	36	48	39	37	32

Remarks: No cases of Asiatic cholera, glanders, plague or yellow fever during the past seven years.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

EDITED BY RICHARD C. CABOT, M.D.

CASE 21041

PRESENTATION OF CASE

A fifty-seven year old physician was first examined approximately three years before his death.

At that time his blood pressure was 190/110 and his weight 195 pounds. His physician put him on a diet and he lost approximately 20 pounds. During the next two years his systolic blood pressure varied between 150 and 190 and, on one occasion, was 135. The diastolic pressure never was below 100, usually running in the neighborhood of 110 and 115. Several nonprotein nitrogen determinations of the blood varied between 30 and 37 milligrams per 100 cubic centimeters. A blood sugar determination was normal. In thirty urine analyses a slight trace of albumin was always present. The sediment showed rare hyaline and granular casts. The blood Wassermann test was negative. His heart had not been enlarged to the usual clinical signs, but these were never definite because of his massive chest and unusual muscular development. Approximately two weeks before the onset of his present illness a routine examination showed a blood pressure of 200/120 and normal urine with the exception of a small trace of albumin. His weight was 188 pounds. About a week later he noticed that he tired very much more easily, did not feel very well, but did not quite know how to describe his feelings.

On the evening before the onset of his present illness he made a short automobile trip and returned home feeling well. The following morning he made several professional calls. At 10 a. m., while in a friend's cellar about to pick up a box, he felt a very severe substernal pain radiating into the back between the shoulder blades, to the thighs and to the left upper jaw, but not to the arms. At once he felt very weak, had cold perspiration and started for home in his automobile. Because of severe weakness and pain he stopped on the way for some brandy but finally reached home and went to bed. The pain eventually resolved itself into a precordial tension and a feeling as though a rope were tied around his chest.

When seen immediately following this attack his blood pressure was 136/70, his pulse 84, and an occasional extrasystole was felt. There were several long periods when almost no pulse could be felt. An increased breadth of the cardiac dullness could not be demonstrated. The sounds were muffled, but a diastolic murmur was heard in the pulmonic area especially below the third rib. A blowing systolic murmur was also heard. A2 was much less sharp than P2. His temperature was 100°, and his white blood cell count was 18,200. He was given morphine with atropine at 2 and again at 5 p. m. The severe pain stopped at about 3 p. m., having lasted five hours, although a sense of soreness in his chest persisted. He was able, however, to sleep a little during the afternoon. A cardiac consultant saw him later that same day and found the maximal apex impulse in the fifth interspace 10 centimeters to the left of the midsternal line, the midclavicular line being 9 centimeters to the left. The sounds were of good quality. A2 was increased. A moderate systolic murmur was heard at the apex and a slight one at the base. There was also a very slight early diastolic murmur all along the sternum. No thrill or friction rub was heard. The rhythm was normal. The pulse was 70, the blood pressure 140/100. The lungs were clear except for emphysematous breathing and a few râles at the bases. The abdomen was soft. The liver and spleen were not felt. The dorsalis pedis pulsations were felt.

He was given three grains of digitalis that night. The following day his blood pressure was 160/70 and there was no change in the heart findings. His pulse was firm, strong and regular. An electrocardiogram showed normal rhythm, rate 100, low T1, flat T2, high origin with slightly late inversion of T3, inverted P3 and inverted QRS.

On the third day his blood pressure remained about the same. His temperature, which had been 101° the night before, was 99°. The diastolic murmur was more audible over the entire left precordium and the systolic murmur was also present. A2 was less than P2. Half an hour later, after a brief conversation with a friend, his face suddenly became contorted without any cry or warning. He immediately became unconscious and died in a few minutes.

CLINICAL DISCUSSION

DR. PAUL D. WHITE: "About a week later he noticed that he tired more easily and did not feel very well . . ." I believe that was a matter of simple fatigue. He was planning to take a fishing trip when the present illness began.

One's experience would ordinarily justify a preliminary diagnosis of coronary thrombosis in such a case, even though there had been no angina pectoris previously. There may or may not be angina pectoris prior to an attack of coronary thrombosis. Our patient had had no pain, palpitation, or dyspnea, and he felt well enough to plan this fishing trip.

There were several points about the case which made us feel that coronary thrombosis was not to be diagnosed with any certainty and that the more likely diagnosis was dissecting aortic aneurysm. The first point was the radiation of the pain down the back to the thighs. Radiation of pain from coronary thrombosis may be to the back as well as to the jaw, as occurred here, but I have never encountered a case of coronary thrombosis in which the pain was referred below the midback, as in this case, where you note at the beginning of the history, ". . . pain radiating into the back between the shoulder blades, *to the thighs*, and to the left upper jaw, but not to the arms."

The second point which caught our attention rather later than at the very beginning, although it was somewhat impressive even in the first history, was the suddenness of the maximum pain, that is, the pain began as intensely as it was felt later on, which is not true in most cases of coronary thrombosis. In coronary thrombosis the pain may in the course of a few minutes reach its maximum intensity but there are always a few moments of discomfort first before the pain reaches its height. In this particular case there was a feeling as if a sledge-hammer had suddenly struck the chest.

A third point which was of importance in the diagnosis of this case was that the blood pressure, in spite of the severity of the attack, was maintained at a fair level, that is, the systolic pressure dropped only to 136 and the diastolic to 70. He had thus a full pulse pressure with systolic pressure well above 100, which is unusual in a case of coronary thrombosis with pain as severe as in this case.

The fourth and final point which favored the diagnosis of dissecting aneurysm as against coronary thrombosis was the electrocardiogram. This was taken on the second day, and it should have shown much more abnormality if coronary thrombosis had been to blame for such a very severe attack of pain. Total inversion of lead III was present and this may be normal, or it may be consistent with slight coronary insufficiency.

Because of the suspicion of dissecting aortic aneurysm involving the iliac arteries, pulsations in the feet were particularly looked for and were found to be full; I could feel a strong dorsalis pedis pulsation in each foot. That made us somewhat uncertain about the diagnosis of dissecting aortic aneurysm, but nevertheless did not cause us to rule it out.

The significance of the murmurs was not clear, and I do not know that it is clear now. He showed a systolic murmur such as is often found in chronic hypertension at the base of the heart. He also showed a basal diastolic murmur, variable in intensity, the significance of which is not clear, though it sounded like a very slight aortic regurgitant murmur; it is very doubtful if the dissecting aneurysm might have caused it, although the possibility must be borne in mind.

The sudden death on the third day might have been the result of rupture either of the heart or of the aorta, or of sudden cardiac standstill, or of ventricular fibrillation.

Our clinical diagnosis was first, a question of dissecting aortic aneurysm, and secondly, and less likely, a question of coronary thrombosis. It did not seem probable that any other factor such as pulmonary embolism might play a rôle.

DR. TRACY B. MALLORY: Have you anything to add, Dr. Siscoe?

DR. DWIGHT L. SISCOE: One thing that impressed me was the fact that this sudden onset of the pain came just after he had walked down stairs and just before he stooped over to pick up a box. That interested me very much. We ordinarily think of some strain as the cause of pain. This came before it. He did a surprising number of things after the onset of pain, without causing any complete collapse.

DR. P. D. WHITE: I might add that he was a very strong and courageous man and would not give in.

DR. SISCOE: When he was first seen by me he weighed 195 pounds and was a very strong man. He was having very severe basal headaches, but after losing twenty pounds these headaches disappeared. We noticed that when he weighed 180 pounds his blood pressure stayed at about the same level, but increased as he gained weight.

DR. JAMES C. WHITE: Did the fact that the pain skipped his arms, although it went to his jaw, have any influence in making you think it was dissecting aneurysm instead of coronary occlusion? In several aneurysms we have seen here there has been pain in the neck, but none in the arms, as one might expect.

DR. P. D. WHITE: We have occasionally had patients with angina pectoris or coronary thrombosis in whom the pain was referred to the jaw without being referred to the arms, but usually the reference would be to both, if jaw pain occurred at all.

DR. HOWARD B. SPRAGUE: I think we have had rare cases referred to one tooth, without radiation to the arm.

CLINICAL DIAGNOSES

Dissecting aneurysm of aorta?
Coronary thrombosis?

ANATOMIC DIAGNOSES

Dissecting aneurysm of the aorta with rupture.
Hemopericardium.
Chronic mesaortitis, non-specific (Klinge).
Cardiac hypertrophy, hypertensive type.
Arteriosclerosis.

Malignant vascular nephritis.
Glomerulonephritis, acute.
Pulmonary atelectasis, zonal.
Operative scars; both knees and appendectomy.

Pathologic Discussion

Dr. Mallory: The postmortem examination here showed a greatly distended pericardium filled with fresh blood. On opening the pericardium it was evident that the aorta was rather markedly thickened, to perhaps half again its normal diameter, and on making a slight incision into it one entered an apparent lumen and then discovered a second seemingly complete aorta inside the first one. The dissection started with a rent in the intima about three centimeters above the aortic valve and worked downward and backward to the annulus fibrosus and even out a short distance along one coronary artery. In the other direction it extended upward over the arch, out the first three centimeters of the innominate artery, along the entire length of the thoracic and abdominal aorta and finally about six centimeters down each iliac artery. The point of rupture of the external layers in the pericardium could not be determined. It was evidently quite a small one and the leak of blood into the pericardium was presumably a slow one, even though the terminal event was clinically fairly dramatic. As far as I know, the initial dissection in these cases never causes death. There are rare cases on record where the dissected space has become endothelialized and blood has continued to flow through both channels of one of these double aortas, with the patient dying years later of some other disease. That is very unusual. The ordinary thing is for the outer layer of the aortic wall to rupture. If the rupture is close to the base of the heart it would probably be into the pericardial cavity; if it is a little farther down the thoracic aorta, into the pleural cavity; and if it is in the abdominal aorta it ruptures into the abdominal cavity, like the case Dr. Sprague discussed a few weeks ago.* These cases of dissecting aneurysm, I think it is fair to say, are never due to syphilis. A certain proportion are due to pure arteriosclerosis, usually in very elderly individuals. Another quite large group is consequent to media necrosis cystica, which Erdheim has described, and since that occurs at any age it is possible to have dissection even in the twenties, although the usual age is fifty or sixty. This aorta showed extensive arteriosclerosis. It did not show anything characteristic of media necrosis cystica. It did show, however, a very marked aortitis of a type that has been described by Klinge of Leipzig in cases of malignant hypertension, which is sometimes almost indistinguishable from rheumatic aortitis, histologically. Since the hypertension clinically and the necrotizing arteriolitis of the kidneys all point to a fairly malignant form of hypertension, I think we can assume that the aortitis in this case fits in that group. It seems probable that a weakening of the media during the development of the aortitis was the underlying cause of the condition.

Dr. P. D. White: I have here Shennan's monograph about which Dr. Bland has spoken. It is a review of 300 cases. They are nearly all postmortem records, not accompanied by clinical notes, sometimes the specimens have been found in medical museums without any adequate history; but there are a few instances where histories are included. There is a summary of symptoms and clinical signs that fit more or less with this case and other cases that we have seen. There is particular note of occlusion of the branches of the aorta by the dissection of the aortic wall. A few points in summary are that the condition is most common in the male sex in the fifties, that syphilis is only rarely the cause, that weakness in the media is primarily responsible, and that hypertension is usual but not invariable. Immediate survival is only once in four times, and in some of these cases with longer survival, there is an establishment of a double aorta. It is important because of the poor prognosis to distinguish this condition as quickly as possible from coronary thrombosis, where the prognosis is much better. The immediate prognosis in coronary thrombosis is favorable in about three out of four cases, whereas in dissecting aneurysm it is less than one out of four. The history is very obscure in some cases. It is conceivable that there may be electrocardiographic changes if the dissection involves and compresses the coronary arteries. Whether or not the slight change in lead III in our case was due to compression of the right coronary artery we cannot say. X-ray evidence is bound to be inconclusive in the great majority of cases.

A Physician: In what portion of the aortic wall does the plane of dissection usually occur?

Dr. Mallory: It is almost always in the midportion of the media. Muscle fibers can regularly be found on either side as was the case here. The degree of dissection was maximal on the posterior aspect of the aorta, so that the outer layers of the aorta had been stripped back over the intercostal arteries for nearly a quarter of an inch. There was, however, no evidence of occlusion of any of these vessels.

*Case 21011, New Eng. J. Med. 212:26 (Jan. 3) 1935.

CASE 21042

Presentation of Case

A fifty-one year old American male schoolteacher on the morning of admission had a sudden, rather terrific, dull pain in the entire lower abdomen and pelvis which "seemed to go all over him", but especially to both legs, upper part of chest and both shoulders. At the same time he had a desire to go to stool, got up and went to the bathroom. Within what he estimated to be five minutes after the onset of the pain he was completely paralyzed from his waist down. The numbness began in his feet and rapidly ascended to a point just above the symphysis. The pain in the chest and shoulders soon disappeared, but that lower down, particularly across the pelvis, persisted. There was no nausea or vomiting. His blood pressure taken by his physician was 140 systolic.

His health had always been good. There was no history of rheumatic fever, precordial pain, or shortness of breath. There had been no trouble in walking and no bladder symptoms. Two days previous to the present illness he had a mild diarrhea which was attributed to his diet.

Physical examination showed a middle-aged man with a pale ashy face complaining of intense pain across the pelvis. There was complete flaccid paralysis of both legs. The feet and lower part of the legs were waxy white in color and very cold. Above this point, extending into a well-defined level between the symphysis and umbilicus, the skin was bluish red and fairly warm, but cooler than the normal skin. No pulsation could be felt in the dorsalis pedis or femoral artery on either side. The heart showed a short, rather high-pitched systolic murmur heard best in the aortic area but transmitted as far as the apex; there was no thrill. The blood pressure was 220 systolic. The abdomen was not tender or rigid. The tendon reflexes in the arms were present and equal. The knee jerks and ankle jerks were absent, and the plantars showed no response. There was anesthesia to pinprick below the upper part of the thighs and in the areas supplied by the sacral segments. The patient said that he had no feeling in his legs and could not tell where they were.

The temperature was 100.5°, the pulse 75. The respirations were 20.

A lumbar puncture showed an initial pressure of 50 which rose slowly to 220 upon jugular compression and gradually fell upon release. The fluid was clear. When the needle was inserted into the spinal canal the patient said that he felt pain in his foot. He was immediately taken to the operating room.

Differential Diagnosis

Dr. Robert R. Linton: We have a fifty-one year old man who suddenly had severe lower abdominal pain which extended chiefly down into the pelvis and into his legs. It is interesting to note that he complained of pain in the chest and both shoulders, and also that he had to go to stool. The paralysis and numbness which came on very quickly, I feel, are also of importance.

In going over this case and considering the history and physical examination, it is obvious what he had wrong with him; I think it is not so obvious what caused it. It must have been that he had arterial occlusion, most likely at the bifurcation of the aorta or higher. His story is consistent with arterial occlusion. He first noticed pain and then numbness—that is usually the order in which we see these symptoms—and later on he developed paralysis. He also was anesthetic to pinprick over his legs, which one always finds in arterial occlusion at the bifurcation of the aorta. I think the blood pressure is of interest. His local doctor noted that it was 140 systolic and when he arrived at the hospital it was 220 systolic. This change indicated that the arterial tree had been cut down to some extent and he had a compensatory hypertension. The fact that the skin was bluish red and fairly warm halfway between the umbilicus and symphysis points to an obstruction at the bifurcation of the aorta. As a rule with a "rider" embolus at the bifurcation of the aorta one sees some discoloration of the skin over the lower abdomen.

Apparently they were questioning his neurological signs and did a lumbar puncture, which as far as I can tell was perfectly normal and certainly showed no block. The fact that he complained of pain in his foot during the lumbar puncture is probably due to the fact that the needle was inserted into the sensory tract in the spinal cord leading from the foot.

I cannot tell from his cardiac findings whether there was anything abnormal in the heart. The heart is the most common site for the origin of arterial emboli. It seems unlikely to me, however, that the heart was the origin of an embolus in this case.

The other thing that one must consider is that this picture may be produced by a dissecting aortic aneurysm which would occlude the aorta above the iliacs. However, I do not think I can make that diagnosis. As far as I can go is to say that he had arterial occlusion at the bifurcation, or slightly higher, due either to an embolus or a dissecting aneurysm.

Clinical Discussion

Dr. Leland S. McKittrick: He had what we interpreted as obvious signs of occlusion of

the arterial tree at or above the bifurcation of the aorta. We were unable to explain it. We thought that it was most likely due to an embolus; from whence it came we did not know. We were disappointed that careful exploration of this region through the femoral on each side failed to reveal any evidence of embolus. We were likewise unable to demonstrate any other cause of the obstruction.

A PHYSICIAN: What explanation did you have in mind for the pain in his chest and shoulders?

DR. MCKITTRICK: It was not explained.

DR. TRACY B. MALLORY: Dr. Viets, have you any comment?

DR. HENRY R. VIETS: I am not entirely familiar with the effect upon the spinal cord of a block in the abdominal aorta. There are many symptoms in this case pointing to a lesion of the lumbosacral spinal cord, for, indeed, the picture is not unlike that which we find in transverse myelitis. The sphincter dysfunction and the level of anesthesia speak strongly for such a localized lesion. We know little about the effect on the spinal cord of cutting off the blood supply from the aorta. I should not be surprised, therefore, if, in addition to the findings in the abdominal aorta, some evidence of a lesion in the spinal cord itself were disclosed by the autopsy.

CLINICAL DIAGNOSIS

Embolus of aorta.

DR. ROBERT R. LINTON'S DIAGNOSIS

Embolus of aorta.

ANATOMIC DIAGNOSES

Dissecting aneurysm of the aorta.
Media necrosis aortica cystica.
Arteriosclerosis.
Dorsolumbar scoliosis.
Aortic stenosis (arteriosclerotic).

PATHOLOGIC DISCUSSION

DR. MALLORY: It is possibly a little unfair to take this case last, since it is a very old one and some of you probably have heard it before. It is another case of dissecting aneurysm, almost identical in its anatomic findings with the preceding case. The process extended the entire length of the aorta, down the right coronary artery for 1.5 cm., down both iliac arteries, but at that point instead of breaking into the lumen as it ordinarily does the process had lifted the intima up so far and pressed the two layers of intima so closely together that occlusion was produced. The effect was that of a valve formation in each iliac artery. The process in this case had caused rather extensive occlusion of other vessels, too. Whereas in the first case all the arteries coming off the aorta apparently remained patent, in this case not only the two iliacs but also the inferior and superior mesenteries were completely occluded. He lived long enough so that small thrombi developed just beyond the point of occlusion in each artery.

DR. PAUL D. WHITE: Were they occluded in the same way that the iliacs were?

DR. MALLORY: Yes.

A PHYSICIAN: In the first case what was the state of the iliac arteries?

DR. MALLORY: At the lower end of the dissection, rupture into the lumen had occurred, so that the blood was pouring out freely.

I think there is no doubt, as Dr. Viets suggested, that some of the arteries to the spinal cord certainly must have been occluded in this second case. Although we did not have permission to do the cord, I think there is no question that it would have shown degeneration in its lower segments.

This case, incidentally, showed a very typical histologic picture of media necrosis aortica cystica.

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HOME CARE FOR CHILDREN WITH HEART DISEASE

RECENT advances in our knowledge concerning rheumatic fever and its important complication, rheumatic heart disease, have emphasized two factors of major importance in managing these patients. First, rheumatic fever is a generalized systemic disease, essentially chronic in nature. It may persist for months or even years usually as a low-grade and for the most part subclinical infection. Recrudescences or recurrences of the symptoms and signs of an acute illness are prone to appear from time to time, often brought to the clinical level by preceding tonsillitis or respiratory infection. Secondly, it is evident from careful follow-up studies of these patients that progression in heart disease, when it occurs, takes place during the time of active rheumatic infection.

The problem in treating this prevalent and disabling disease of childhood is in large measure similar to that which has proved effective in dealing with another chronic infection namely, tuberculosis. Long bed rest is essential. Two or three weeks in bed, until the acute manifestations of the disease have subsided, have proved to be inadequate, and relapses are frequent when patients are allowed up too soon. Several months or even one or two years in severe cases may be necessary before all clinical and laboratory evidence of active disease subsides.

The facilities of our large general hospitals are limited and, hence, available only during the acute stages of the disease. In Boston notable service has been rendered by the House of the Good Samaritan in providing long bed care, as well as intensive study, for many of these patients. The greatest burden, however, in arranging suitable convalescent care in the majority of instances has fallen upon the social service departments of the general hospitals, for it is among the poorer class that rheumatic fever most frequently occurs. During the past twenty years a group of interested and charitable women working as the Committee for the Home Care of Children with Heart Disease in close coöperation with the Cardiac Clinic of the Massachusetts General Hospital has provided facilities in the homes of many of these children whereby long bed care, otherwise impossible, has been made available. Under social service supervision, instruction by craft workers and tutoring by volunteer teachers have been important parts of the program and have served to insure the coöperation of both the patient and the family through many months of bed rest.

It is with a feeling of satisfaction that the medical profession learns that recently the Children's Mission to Children on its eighty-fifth anniversary has announced its association with the Committee for the Home Care of Children with Heart Disease in a plan to elaborate and carry forward the work already in progress. Suitable cases of rheumatic fever and rheumatic heart disease requiring prolonged rest in bed will be selected by the Cardiac Clinic of the Massachusetts General Hospital. The homes of these individuals will be investigated by capable social workers and when possible bed care will be arranged in the patient's own home. If the home conditions are inadequate for prolonged convalescence or a change of environment seems desirable, foster homes will be utilized until suitable adjustments can be made, or until improvement in the patient's condition warrants treatment with supervision at home. Occupational therapists will determine the patient's interests and provide instruction along lines best suited to the possible future limitations of the individual case. Visiting teachers will aid in keeping up the children's school work. Medical supervision will be directed from the clinic, but necessary medical home visits will also be arranged.

It is to be hoped that not only will a service, otherwise unavailable, be rendered this unfor-

tunate group of children, but also that valuable information of both medical and public health interest will accumulate. It seems appropriate that the Children's Mission and the Committee for the Home Care of Children with Heart Disease should be associated in this important work.

PUBLIC HEALTH VERSUS PUBLIC HEALTH

ALTHOUGH the policy of the *Journal* has always been to remain mutely on the sidelines when wordy battles are waged on the governmental gridiron and to dabble not in the muddy stream of politics, there are nevertheless occasions when the eloquence of silence seems scarcely vociferous enough to comment on the vagaries of human political behavior. Thus we learn from an esteemed contemporary in the broad field of daily journalism that a neighboring city, famed largely as a centre for the manufacturing of jewelry, has recently elected a new mayor on a two plank platform; one plank calling for the removal of discarded car rails from the city streets; the other to end the rule requiring that all milk be pasteurized.

The removal of obsolete car rails from the city streets may well be an example of wise and practical statesmanship, even if not on the loftiest plane, and perhaps a constructive public health measure as well, especially if the rails stand high enough above the accepted and orthodox street level to fling unsuspecting citizens beneath the wheels of swift Juggernauts of rapid transportation. A pledge to end pasteurization of milk, however, seems to us, in our blind devotion to human welfare, to force municipal politics to a new low level.

It undoubtedly shows a lack of sophistication, but for many of us there is a recurring amazement when public health is found again to be the football in a ballot-seeking game, and expediency to take the place of altruism. The stream of politics is indeed a sullied one. And perhaps, after all, the mayor-elect was merely trailing a red herring across the path of civic virtue. Platforms are built as places from which to exhort the multitude, not as floors upon which the real work of life is done.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

JACKSON, HENRY, JR. A.B., M.D. Harvard University Medical School 1919. Associate Physician, Thorndike Memorial Laboratory and Assistant Visiting Physician, Boston City Hospital. Associate Physician, Collis P. Huntington Memorial Hospital. Assistant Professor of Medicine, Harvard Medical School. Address: Boston City Hospital, Boston, Mass. Associated with him is

PARKER, FREDERIC, JR. A.B., M.D. Harvard University Medical School 1916. Pathologist, Boston City Hospital. Associate Professor of Pathology, Harvard Medical School. Address: Boston City Hospital, Boston, Mass. Their subject is "Agranulocytosis: Its Etiology and Treatment." Page 137.

MOORE, GEORGE A. S.B., M.D. Harvard University Medical School 1911. F.A.C.S. Surgeon, Moore Hospital, Brockton. Consulting Surgeon, St. Luke's Hospital, Middleboro; Lakeville Sanatorium, Lakeville; Bridgewater State Hospital and Plymouth County Hospital. His subject is "Bleeding Gastric Ulcer." Page 149. Address: 167 Newbury Street, Brockton, Mass.

FALSEY, EDWARD F. B.S. Candidate for M.D. degree at the Yale University School of Medicine; Junior Interne, Rhode Island State Hospital for Mental Diseases, June-September, 1934. His subject is "Typical Epileptic Seizures in the Course of Schizophrenia: A Report of Two Cases." Page 153. Address: Sterling Hall of Medicine, New Haven, Conn.

WILLIAMS, JOHN T. M.D. Harvard University Medical School 1904. F.A.C.S. Surgeon-in-Chief for Obstetrics and Gynecology, Boston City Hospital. Instructor in Gynecology, Harvard Medical School. Obstetrician-in-Chief, Chelsea Memorial Hospital, Whidden Memorial Hospital and Winthrop Community Hospital. His subject is "Primary Carcinoma of the Vagina." Page 156. Address: 429 Beacon Street, Boston, Mass.

SWICK, M. M.D. Columbia University College of Physicians and Surgeons 1924. His subject is "General Considerations and Principles of Excretion Urography." Page 158. Address: 133 East 58th Street, New York, N. Y.

TYZZER, E. E. Ph.D., M.A., M.D. Harvard University Medical School 1902. George Fabyan Professor of Comparative Pathology, Harvard Medical School. His subject is "Theobald Smith." Page 168. Address: Harvard Medical School, Boston.

THEOBALD SMITH

JULY 31, 1859—DECEMBER 10, 1934

BY E. E. TYZZER, M.D.

THE career of a great man has ended but his contributions to science will long serve as foundation stones for the structure of our understanding of disease and its transmission. Those who have been in any way associated with Dr. Smith cannot but feel that they have been highly privileged and that the fullness of their lives has been enhanced thereby. The chief events of his career are well known and need only be briefly reviewed. A graduate of Cor-

nell University, he took the medical course at the Albany Medical College of Union University, receiving the degree of Doctor of Medicine in 1883. A year later we find him at the recently organized Bureau of Animal Industry at Washington, the staff of which then consisted of Salmon in the capacity of director, Smith, Kilborne and a Negro helper. He began his work here in a period in which a succession of epoch-making discoveries were being made in reference to etiology, transmission and control of infectious diseases. Pasteur had already devised methods of immunizing animals against anthrax and was soon to put his anti-rabies inoculation to test. Koch had cleared up the etiology of anthrax and had shown the part played by spores in its transmission. He had also discovered the tubercle bacillus, thus definitely establishing tuberculosis as an infectious disease. Laveran had described the micro-örganisms of a malarial fever, while Patrick Manson had only recently shown that mosquitoes served as intermediate hosts in filariasis. There is reason to believe that Smith was in a way a disciple of Koch, at least he adopted the same critical and thorough-going methods of investigation rather than the more or less haphazard methods of Pasteur. In the course of his earlier work, he discovered the hog cholera bacillus, later showing the relationships of various bacteria of the paratyphoid-enteriditis group to which this belongs. With Salmon he demonstrated that products of bacterial growth could be utilized in producing immunity.

The masterpiece of his long series of contributions soon followed. In 1888 he was directed by his chief to work on the problem of Texas Fever in cattle. This work was done in collaboration with Kilborne, and while it is apparent that valuable suggestions as to the mode of transmission of the disease were furnished by Kilborne and were forthcoming from various other sources, especially from the cattlemen themselves, there is no doubt that we owe the first actual demonstration of the rôle of an arthropod in the transmission of an infectious disease to Smith's painstaking and thorough methods of research. The Texas Fever report has set a standard for accuracy and fullness of treatment that would be difficult to excel and not only furnished the basis for the control and prevention of this scourge in cattle, but also paved the way for the elucidation of the transmission of insect-borne diseases, such as malaria, yellow fever, sleeping sickness, bubonic plague, and infections of the typhus group. If this were Smith's only contribution to medical science, he might have been justifiably proud of his accomplishment, but this marked only the beginning of a long series of important researches. While still at Washington, he noted the differences between the human and bovine strains of tuberculosis, discovered the protozoön of blackhead in turkeys, and investigated the possibilities of immunization through the inoculation of killed bacteria. While at Washington, he held the Professorship of Bacteriology at the George Washington (at that time the Columbian) University.

Theobald Smith was called to Harvard in 1895 through the coöperative efforts of the University and the Massachusetts State Board of Health, being made Professor of Applied Zoölogy and given charge of the production of smallpox vaccine and diphtheria antitoxin for the State. A year later, following the endowment of the chair of Comparative Pathology by Mr. George Fabyan, he became the first Professor of that department. After a period spent in Europe in visiting institutions engaged in the production of vaccines and sera and in studying methods, he established and organized the State Antitoxin Laboratory at Forest Hills. Located at first in the old Bussey Institution and provided with meager equipment, eventually a well-planned and up-to-date laboratory was built with facilities also for the care of inoculated animals. There are doubtless many physicians who have little realization of Smith's contributions to public health in Massachusetts and of the amount of study and constant supervision required for the production of safe vaccine and antitoxin. Not only were these products uniformly efficient but there were no accidents throughout his twenty years of service.

During this period he was gradually building up the subject of Comparative Pathology. It is probably rather unusual for the medical student as he studies the subjects of Anatomy, Physiology, Pathology, etc., to realize what they are all about, but those who at the old school on Exeter Street, took Theobald Smith's optional course in "The Comparative Etiology of Infectious Diseases" could scarcely fail to see the light. The disjointed subjects which they had been studying suddenly fell into place and for the first time a conception of disease as a whole dawned upon the mind. We need to scarcely more than enumerate the more important of Smith's subsequent contributions, most of them are so well known. His early work on anaphylaxis (anaphylaxis in the guinea pig for a time being referred to as the "Theobald Smith phenomenon") being basic to much of our present understanding of hypersensitivity, the rôle of sugars in the cultivation of bacteria and in the production of their toxins, the fermentation tube and finally the demonstration of the immunization properties of the toxin-antitoxin mixture which in recent years has been so widely utilized in immunization against diphtheria. The origin of epidemics of septic throat from the milk of cows infected with a streptococcus of human origin was elucidated through his studies and those of his collaborators. In his laboratory it was demon-

strated that milk of cows infected with *Bacillus abortus* could produce disease in guinea pigs.

Among Smith's personal friends at Harvard were Charles W. Eliot, Henry P. Wolcott and Frederick C. Shattuck, who were instrumental in bringing him to Harvard and in establishing his department and who continued thereafter his enthusiastic supporters. Marshal Fabyan also remained a personal friend throughout his life. It would appear, however, that Simon Henry Gage, his old professor of physiology at Cornell, was the only one who could be regarded as a real intimate friend. For Professor Gage's visits great preparations were made, and these occasions were characterized by reciprocal back clappings and an atmosphere of general relaxation and good fellowship. On the other hand, his admirers were legion and were widely distributed throughout many countries of the world. For the extent and sincerity of this admiration, one only needs to recall the speeches of the distinguished men who were gathered at his Farewell Dinner on June 2, 1915, or read the letters and cablegrams that came from abroad. Many will recall the great gathering at this Farewell Dinner coming at the end of twenty years of service to Harvard and the State, the humorous, illustrated place-cards entitled "Thanks to you, Theobald Smith" prepared by Fabyan, and the unveiling of the basrelief of Smith made by Bela Pratt.

In reviewing the career of a great man, it is perhaps fitting to consider some of his outstanding characteristics. Smith was of a modest, retiring disposition, not especially robust but showing a great amount of energy in his investigations and in attention to the business of his department. Throughout his life he found relaxation in music, of which he was very fond; he played the piano until recently when a stiffening of his fingers finally interfered. He was in no sense aggressive by nature but courageous when occasion demanded. It is well recognized that he was critical of evidence presented by other investigators, relying chiefly upon that of his own observation. It was doubtless on this account that he failed to attract the following of students that might have been expected. On the other hand, his influence was widely felt and the young investigator found him approachable, sympathetic and stimulating. One never left an interview with him without a feeling of exhilaration and a sense of having profited thereby. The problems that he chose to work upon were almost invariably utilitarian in character, that is they were undertaken with the view that they might eventually prove useful to mankind. Whether the major success attending his being allotted the practical problem of Texas Fever early in his career influenced him in this respect, we cannot say. Having launched upon a problem, the utilitarian objective did not blind him to great principles. Furthermore what he regarded as practical problems would probably be considered by others as more or less academic in nature. Another characteristic of his work was the meticulous care with which he recorded observations and data. It was not his custom to use large series of animals in his experimental work, but his record of each animal was complete as to pedigree, identification and all the known circumstances of the experiment. With his keen mind, quick to see the significance of results, and with the care with which he planned and checked his experiment, large series were not essential to him. Thus he did not resort to any great extent to statistical evidence; his methods were simple and direct. Unlike many investigators who apply themselves so closely to their subject that they lose perspective, Smith had the faculty of fitting the parts together and of seeing their relationship to one another in the picture as a whole. He was not one to limit himself to a single method or technique, but utilized different methods in order to check one by the other. Shoddy work, slipshod thinking or dishonesty in any form, he could not tolerate. His ability to generalize led him to make many addresses and to write many papers pertaining to the subject of disease. Smith went in 1911 to Berlin as Exchange Professor from Harvard and acquired the respect and admiration of a large following of German scientists.

It is a matter of gratification to those who have followed Smith's work that toward the close of his life he should have collected together his views on disease in a book entitled "Parasitism and Disease." This work is based on his Vanuxen lectures with some expansion and the addition of several chapters. It shows as might be expected of one of advanced years, some faults, but nevertheless presents a great amount of pertinent material in a simple manner that may readily be understood by the student or layman. In this is summed up his conception of disease processes and thus furnishes a fitting culmination to his life's work.

It is probably not generally known that in 1902, Dr. Smith was invited by the Board of Directors of the Rockefeller Institute to accept the directorship of a department for the study of animal diseases. The foremost of several reasons which he gave for declining this offer was "a strong sense of gratitude toward the President and Fellows of Harvard University and Mr. George Fabyan for the sacrifices they have made in founding and maintaining the Chair of Comparative Pathology, which is only now beginning to show signs of fruitage." It is of interest that Smith at this time outlined what he considered was essential to the organization of such a laboratory. Thirteen years later, he was induced to accept the Directorship of the Department of Animal Pathology of the

Rockefeller Institute for Medical Research, at Princeton, New Jersey, the establishment and organization of which required several years of earnest effort. It is no secret that this project was undertaken by the Rockefeller Board of Directors with the confidence, although without positive assurance, that Dr. Smith might be secured to take charge of the new work, so that this department might be considered to be established for him. Thus, it is seen that he was actually concerned in the building up of the United States Bureau of Animal Industry and in the creation of the Massachusetts State Antitoxin Laboratory, the Department of Comparative Pathology at Harvard, and the branch of the Rockefeller Institute of Medical Research at Princeton, New Jersey devoted to animal diseases. With advancing years, he eventually asked to be relieved of his administrative duties but continued his interest in research work. Notable among his later contributions was the demonstration of the importance of colostrum in the resistance of the new-born to bacterial infections. With unimpaired mind, he maintained an active interest in scientific matters and affairs. We find him only a brief time ago in his summer home at Silver Lake, New Hampshire, keenly enjoying life and laying plans for future work. Thus at last what more fitting than to repeat in farewell the title bestowed by Dean Bradford, "Theobald Smith, a prince of scientists."

MASSACHUSETTS LEGISLATIVE NOTES

H. 114 under the title "An Act relative to the Holding of Inquests in Case of Deaths by Violence and Otherwise" provides for an amendment of Chapter thirty-eight, section eight, of the General Laws, Tercentenary edition, as amended by chapter one hundred and eighteen, that the attorney general or the district attorney may require an inquest to be held in case of any death caused by external means, notwithstanding that no other action has been taken. The procedure is defined in the bill.

H. 61 provides for an amendment to Section one hundred and seventeen of the General Laws to read as follows:

SECTION 117. Each city or town shall provide for treatment, either in a hospital or as out-patients, of indigent persons suffering from gonorrhea or syphilis.

H. 60 provides for an amendment to Chapter seventy-six of the General Laws which will, if enacted, prevent the admittance of a pupil to a public or private school except upon presentation of a physician's certificate that the child has been vaccinated. This is in substance a continuation of the campaign carried on for so many years by Dr. S. B. Woodward.

H. 47 contains recommendations of the Commissioner of Mental Diseases to the effect that the name of the Gardner State Colony should be changed to the Gardner State Hospital because it is now organized to give the same standard care to mental cases as is provided in the other State Hospitals of the Commonwealth.

In addition, the recommendation is made that section 19, chapter 123, of the General Laws, be repealed, thus placing the supervision of family care patients upon the hospitals that are properly charged with such supervision.

H. 27 contains the recommendations of the Commissioner of Education which are in substance to advance the age at which minors may be legally employed from fourteen to sixteen years of age, and requires that minors between the ages of sixteen and seventeen shall be in school or at work properly certified.

Increase of grade educational requirements, except in case of mental or physical deficiencies, two or more grades to the completion of the eighth grade, or eight years at school (now seven years at school).

Open the continuation school for full-time attendance in employment preparation classes of minors.

Increase the required number of days of elementary school from 160 to 180.

The transportation of physically handicapped children.

Raising the appropriation for printing material to be used in connection with the physical examinations of school children to committees and boards of health to $1200.

Additional facilities for the education of the blind.

Recommendation for a change in the law which will prohibit pupils from directing vehicular traffic.

A change in chapter 73 of the General Laws which will permit the Department to confer the degree of Master of Education in the State Teachers Colleges and that the Lowell Textile Institute may be given the right to grant degrees of Master of Science in Textile Chemistry and in Textile Engineering.

H. 122 provides for an amendment to chapter 260 of the General Laws as further amended by chapter 318, which will confine actions of tort for malpractice, error or mistake against physicians, surgeons, dentists, optometrists, hospitals and sanitaria, to a period within two years next after the action accrues and for various other causes specified in the bill.

H. 161 will, if enacted, prevent sulphur dioxide or any of its compounds in meat or meat products offered for sale.

MISCELLANY

MORTALITY RATES

Telegraphic returns from 86 cities, with a total population of thirty-seven millions for the week ending January 12, indicate a mortality rate of 14.0

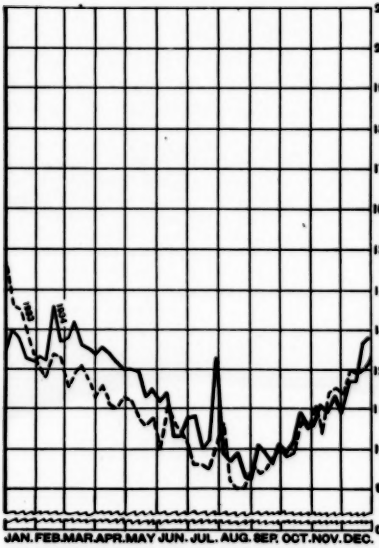
as against a rate of 12.8 for the corresponding week of last year. The highest rate (27.7) appears for Nashville, Tenn., and the lowest (9.0) for Milwaukee, Wis. The highest infant mortality rate (16.2) appears for Nashville, Tenn., and Omaha, Nebr., and the lowest for Bridgeport, Conn., Canton, Ohio, Spokane, Wash., Syracuse, N. Y., and Waterbury, Conn., which reported no infant mortality.

The annual rate for 86 cities is 13.8 for the two weeks of 1935, as against a rate of 12.9 for the corresponding period of the previous year.

SUMMARY OF DEATHS AND DEATH RATES (ANNUAL BASIS) FROM AUTOMOBILE ACCIDENTS PER 100,000 ESTIMATED POPULATION FOR 86 CITIES FOR CORRESPONDING PERIODS OF 1935 AND 1934

	Week ending Jan. 12, 1935	Jan. 13 1934	First 2 weeks 1935	1934
Total deaths	192	191	420	387
Death rate	26.8	26.6	29.3	27.0
Deaths due to accidents in city	160	166	356	322
Death rate	22.3	23.1	24.8	22.4

DEATH RATE PER 1,000 POPULATION OF CITIES REPORTING FOR 1934*



*Department of Commerce, Division of Vital Statistics.

CORRESPONDENCE

AN URGE TO ACTION

Dr. William H. Robey,
President, Massachusetts Medical Society,
Dear Dr. Robey:

In the January 10 issue of The *New England Journal of Medicine* there appeared an editorial and a letter from Dr. Miles calling attention to the bill to be introduced by him at the present session of the Legislature.

The need, or at least the desirability of such legislation, should prompt united action on the part of the profession; and in this connection there occur to me two thoughts which I am passing along to you, viz.:

1. How may one know when a hearing is to be held?* Would it be possible to have this information published in the *Journal* so that all readers might be able to plan to attend?

2. The Secretary of each District Society might obtain the signature of each of his members on a petition or on form letters, these petitions or form letters to be placed in the hands of the Chairman of the Committee on State and National Legislation to be used by him at the hearing; and copies of the same forwarded to the members of the Legislature representing the several districts.

I am writing this latter thought to Dr. A. H. Blake, President of Middlesex South District, and am enclosing a copy of my letter.

Very truly yours,
L. G. RONDEAU.

555 Washington St., Brighton, Mass.

*EDITORIAL NOTE: For the information of the writer of the letter to Dr. Robey, notices of hearings often appear in the daily papers, but not always, and this *Journal* seldom has such notices early enough for publication in advance of the hearings. If any doctor is desirous of attending the hearing on Dr. Miles' bill, if he will ask his Representative or Senator to keep him informed of the date, he will probably be notified in time.

SOCIAL INSURANCE

December 29, 1934.

Editor, *New England Journal of Medicine,*

A meeting on Social Insurance arranged by the League of Medical and Allied Professions was held at the Boston Medical Library on December 17, 1934. Mrs. Dorothy W. Douglas, assistant professor of economics at Smith College, was the speaker of the evening. Mrs. Douglas brought out the fact that no Federal Law of any kind exists to meet the present problem of unemployment. A Bill known as the Workers Unemployment Insurance Bill—H. R. 7598, has been introduced in the United States Congress and has been the subject of discussion by various groups including industrial workers, farmers, professionals, etc. The main features of the Bill are as follows:

1. Unemployment Insurance should cover all involuntary unemployment in all wage-earning or salaried occupations or self-employment.

2. It should cover all unemployment, whatever the

cause — industrial changes, occupational accidents, sickness, maternity, or old age.

3. It should prevent lowering of standards of living by providing not a "dole," but amounts equal to average earnings in the trade or profession.

4. Its administration should be in the hands of the insured.

5. The source of funds should be the higher individual and corporate incomes, and not the working population; with consequent transfer of purchasing power from channels of investment to channels of consumption.

It is assumed that professional and expert services will be provided under the provisions of the Bill. As to the exact nature of such provisions it would seem that in the field of medical care and treatment it should be none other than the medical profession itself that should take a hand. The medical opinion elicited at the meeting (possibly, because of the inexperience of the chairman) did not contribute materially to the clarification of medical points involved in the Bill. However, it was decided at the meeting that a committee be appointed by the chairman to study the Bill from the point of view of its medical implications. It was expected that a delegate from this group would probably be present in Washington at the National Congress for Unemployment and Social Insurance which meets on January 5, 6, 7, 1935.

RUTH WEISSMAN, M.D., *Chairman.*

311 Commonwealth Avenue,
Boston, Mass.

ON LOUSINESS, AND THE ORIGIN OF THE COMB

Editor, *New England Journal of Medicine,*

Many of the readers of the *Journal* have probably seen Dr. Zinsser's fascinating article on "History and the Louse" in the January number of the *Atlantic.*

In connection with this subject it is of interest to recall that, according to Cabanès,* it was to this swiftly running and slithering little creature that we owe the origin of the comb. He says, "Ah! Cette vermine! Leur en a-t-elle causé du tourment a nos bons aïeux!"

Cabanès continues, telling us that an instrument must be found to act as a remedy for their ravages; from this comes the idea of the comb with strong and long-pointed teeth.

The first combs, we are told, were made from the back bones of fishes. As time went on combs of wood, bone and ivory took the place of the primitive fish combs.

Prehistoric peoples of the entire world, we are told, have made use of the comb, but it must not be forgotten that they were not of common use. For a time they were exclusively reserved for liturgical purposes. The comb was used to straighten and smooth out the surrounding hair of the early Bishops of the Church about the "tonsure". From this the origin of the "peignoir," originally a short gown put about the holy man's shoulders "Quand on le peignait." The priest demanded of God that the comb would "décrassait la tete et la nettoyait de ce qu'il y avait d'impur et de grossier, le Saint-Esprit, par sa grace devine, daignat purifier le coeur de l'officiant et en oter tout ce qu'il pouvait y avoir de contraire a la vertu."

In the time of Erasmus lousiness was the common lot—like the smallpox, and rich and poor were alike infested, but the poor scholars seemed to suffer more than anybody, for Cabanès tells us that Erasmus was a victim when in Paris at Montagu College of the "pouillerie scolastique," this college being, "the poorest, the most democratic of the university houses".

In his "Colloques," says Cabanès, Erasmus makes one of his interlocutors say; "Unde podis?" (Where do you come from?)

"E Collegio Montis Acute." (From Montagu College.)

"Ergo ades nobis onustus litteris?" (You have come back to us then full of literature?)

"Imo pediculis." (Much fuller of lice.)

Very truly yours,

WM. PEARCE COUES, M.D.
12 Monmouth Court, Brookline, Mass.

*Cabanès: Moeurs intimes du Passé, Paris, Librairie Albin Michel, 1908.

ARTICLES ACCEPTED BY THE AMERICAN MEDICAL ASSOCIATION COUNCIL ON PHARMACY AND CHEMISTRY

535 North Dearborn Street, Chicago, Ill.,
January 3, 1935.

Managing Editor,

The *New England Journal of Medicine,*

In addition to the articles enumerated in our letter of November 30 the following have been accepted:

Grisard Laboratories
Chocolate Coated Tablets Scillonin, 0.5 mg.

Lederle Laboratories, Inc.
Diphtheria Toxin for Schick Test in Peptone Solution, fifty test package
Staphylococcus Toxoid

Eli Lilly & Co.
Ampoules Sodium Amytal, 0.065 Gm. (1 grain)
Tablets Amytal, ½ grain

National Drug Company
Diluted Diphtheria Toxoid for Sensitivity Test, 5 and 50 test packages

Winthrop Chemical Co., Inc.
Tablets Skiodan, 1 Gm.

The following products have been accepted for inclusion in the List of Articles and Brands Accepted by the Council But Not Described in N.N.R. (New and Nonofficial Remedies, 1934, p. 443):

Lederle Laboratories, Inc.
Quinidine Sulphate (Lederle)

Capsules Quinidine Sulphate (Lederle) 3 grains (0.2 Gm.)
Capsules Quinidine Sulphate (Lederle) 5 grains (0.325 Gm.)

Yours sincerely,
PAUL NICHOLAS LEECH, *Secretary*,
Council on Pharmacy and Chemistry.

RECENT DEATHS

McKELVEY—ALEXANDER DUNBAR MCKELVEY, M.D., of 160 Bloor Street West, Toronto, Ontario, Canada, a non-resident member of the Massachusetts Medical Society, died January 6, 1935.

He was born in 1885 and graduated in medicine from the University of Toronto Faculty of Medicine in 1908. He was also a Fellow of the American Medical Association.

BELLAMY — WILLIAM WOOLSEY BELLAMY, M.D., of 36 Adams Street, Watertown, died at his home, January 17, 1935. He was born in Dorchester in 1887, the son of William and Anna (Johnson) Bellamy. After two years at Harvard College he entered the Harvard Medical School from which he graduated in 1902. He practiced for a time in Dorchester, but retired to take on the work of medical recorder for several societies.

He joined the Massachusetts Medical Society in 1904 and again in 1923, and was also a Fellow of the American Medical Association. He was employed for a time as stenographer to the Secretary of the Massachusetts Medical Society. His social contacts were especially in the Harvard, the University, and the Charles River Country Clubs.

He is survived by his widow, Mrs. Elsie (Stark) Bellamy; his father, two brothers, Robert of Dorchester and Albert of Jamaica Plain, and a sister, Miss Margaret B. Bellamy of Winthrop.

OBITUARIES

DR. MALCOLM STORER

The death of Dr. Malcolm Storer on January 2, 1935, at the age of 72, removes from this community one of its kindly and trustworthy practitioners and one who, in his social and civic relations, was always a dependable personage. Those who were privileged to know him intimately were attracted by his personal charm, his broad interests, his effervescent humor and his felicity in conversation. The familiar way in which his intimates addressed him, preferring to call him "Mike" rather than Malcolm, was not, I fancy, because it was easier to say, but because it connoted certain of those attractive Celtic characteristics often associated with men of that nationality.

His early training was of a determining factor in much that was significant in his later life. He spent some considerable time abroad with his father at a time when the acquisition of foreign languages was relatively easy, with the result that he was able to read and speak several European tongues readily and this was a great advantage to him personally and enabled him to serve the Boston Public Library's Committee for the selection of books on a good many occasions.

It was during his stay in Europe with his father, who was there for treatment of arthritis, that he formed an early interest in his father's hobby of numismatics, an interest that increased as he grew older and after his father's death he completed and edited the work that he began, publishing a large, single volume, descriptive catalogue of his very complete and valuable collection of medals. Recognition of his outstanding knowledge of this subject came through his appointment as curator of the collections of coins and medals at Harvard University, the Massachusetts Historical Society, the Boston Medical Library and the Boston Art Museum. He had served the Boston Numismatic Society as its Secretary and President.

Without ever neglecting any of the responsibilities in connection with such professional associations as he chose to accept, he was in a position to indulge in purely cultural tastes with which he was so largely endowed and which made him such a delightful companion as well as a very competent adviser in his various public associations. Such men are rare and when they are taken away their loss is felt by the entire community in which they lived. His precollegiate education was obtained in Germany, Italy, England, and Newport, Rhode Island. He graduated from Harvard University in 1885 and true to the family tradition, his father and grandfather both being doctors, he took a medical degree from Harvard University in 1889. His grandfather, Horatio Storer, had large real estate holdings in the Temple Place section of the Boston of his day and for many years his grandson had offices at 476 Boylston Street.

His hospital and teaching connections at Harvard Medical School were in the specialty of Gynecology.

Interest in the cultural aspects of his profession brought him to the service of the Boston Medical Library where he was a member of the Executive Committee for many years by virtue of his office of Curator of Medals. Among the numerous societies of which he was a member may be particularly mentioned the Massachusetts Historical Society and the Naval History Society.

During the World War he served for three years sending supplies to the French wounded and for Italian relief purposes. He was given the rank of Lieutenant in the Medical Reserve Corps.

In 1889 he married Miss Grace Ayrault of Geneva, New York. She, and a daughter, Mrs. Egerton B. Sawtelle, of Augusta, Maine, two brothers and a sister survive him.

DR. JOHN NELSON COOLIDGE

Dr. John Nelson Coolidge died at his home in Ottawa, Ontario, on January 9, 1935, after a long illness. He was born in Leicester, Mass., October 23, 1866, and graduated from Amherst College with the class of 1889, and after a year of teaching, entered the Harvard Medical School graduating in 1894.

He served as medical house officer at the Boston City Hospital and began the practice of medicine in Boston in January, 1895. He was particularly well suited for the care of ill people and won the confidence and devotion of his many patients.

For a few years he was an assistant in teaching Clinical Medicine in the Harvard Medical School. Later he became assistant in the Department of Theory and Practice at Tufts College Medical School resigning in 1910 when he was called to act as home office examiner of the Metropolitan Life Insurance Company in New York. He was made Assistant Medical Director in 1916. His association with the company began as an examiner in Boston in 1898.

In 1924 when the Canadian home office was established in Ottawa, Dr. Coolidge was selected as head of the medical division. In the summer of 1928 he was obliged to relinquish his duties on account of ill health. He will long be remembered by his friends here for his genial disposition, his loyalty and devotion, qualities which also won him many close and appreciative friends both professionally and socially during his short active life in the Canadian capital.

Dr. Coolidge was a member of the Massachusetts Medical Society, the American Medical Association, the Royal Ottawa Golf Club and other societies.

He is survived by Mrs. Coolidge, and a daughter, Miss Marian Elizabeth Coolidge.

RESOLUTIONS OF THE MIDDLESEX EAST DISTRICT MEDICAL SOCIETY ON THE DEATH OF GEORGE FARWELL DOW, M.D.

In Reading where he had practiced his beloved profession for nearly forty years, Dr. George Farwell Dow died December 9, 1934.

Educated in the public schools, at Andover, Harvard College, Harvard Medical School, and at the Boston City Hospital as interne, he returned to his home town and took up the practice of medicine where his father, Dr. John O. Dow, had served the community so well during the previous generation.

During the Spanish War he was Surgeon Major of the Old Sixth Massachusetts and later served in the Philippines. During the World War he was on the Draft Board and then served as Captain in the Medical Service.

As a physician he won the confidence and affection of those with whom he came in contact. Thorough, unsparing of self, honest, humane, he exemplified the "family physician" at his best, and it is worthy of note that the local paper headed its heartfelt tribute "Here was a man."

Doctor Dow had been a member of this Society since 1897, serving in many offices and committees. He was also a Trustee of the John M. Harlow Fund.

The Middlesex East District Medical Society desires to inscribe on its permanent records, its deep sense of loss in his death as well as its grateful appreciation of a good physician, a wise counselor, a genial, loyal friend, and a courteous gentleman. It is recommended that these resolutions be spread upon the records of the Society and that a copy be sent to his bereaved family with our sympathy.

(Signed)

RICHARD DUTTON, M.D.,
E. D. RICHMOND, M.D.,
C. E. ORDWAY, M.D.

NOTICES

LECTURES AND CLINICS ON HEART DISEASE

BY DR. CHRISTIAN

Dr. Henry A. Christian, Hersey Professor of the Theory and Practice of Physic at the Harvard Medical School, began a series of 13 lectures and clinics on heart disease at the Peter Bent Brigham Hospital on January 14. Three lectures of the series have already been given. Subsequent lectures are scheduled for the following dates: January 24 at 3:30 P.M., January 31 at 3:30 P.M.; February 7 at 8:30 A.M. and 3:30 P.M., February 14 at 8:30 A.M. and 3:30 P.M., February 18 at 8:30 A.M., February 21 at 8:30 A.M. and 3:30 P.M., and February 25 at 8:30 A.M. *Note that the afternoon exercises are scheduled for 3:30 P.M. instead of 4:30 P.M., as previously announced.* Physicians are cordially invited.

The subjects discussed will be the following:

1. Physiology of heart in relation to normal and abnormal cardiac function.
2. Symptoms and signs of cardiac disease; varieties of heart disease and their diagnoses.
3. Treatment of cardiac insufficiency with discussion of pharmacological action of chief therapeutic agents used.
4. Special forms of heart disease; angina pectoris and coronary occlusion.
5. Special forms of heart disease (continued); chronic non-valvular heart disease including effects on heart of arteriosclerosis and of hypertension.
6. Special forms of heart disease (continued); chronic valvular heart disease; syphilitic heart disease.
7. Special forms of heart disease (continued); acute endocarditis; acute and chronic pericarditis.

UNITED STATES CIVIL SERVICE EXAMINATION

The United States Civil Service Commission has announced an open competitive examination as follows:

Junior Medical Officer (Interne)
St. Elizabeths Hospital, Washington, D. C.

Applications for the position of Junior Medical Officer (Interne) at St. Elizabeths Hospital, Wash-

ington, D. C., must be on file with the Manager of the Fourth U. S. Civil Service District, Washington, D. C., not later than February 18, 1935.

Full information may be obtained from the Secretary of the United States Civil Service Board of Examiners at the post office or customhouse in any city which has a post office of the first or the second class, or from the United States Civil Service Commission, Washington, D. C.

REMOVAL

BERNARD ZUCKERMAN, M.D., announces the removal of his office to 978 Blue Hill Avenue, Dorchester.

CLINIC AT THE PETER BENT BRIGHAM HOSPITAL

At 3:30 P.M. on Thursday, January 31, in the Amphitheatre of the Peter Bent Brigham Hospital, Dr. Henry A. Christian, Physician-in-Chief, Hersey Professor of the Theory and Practice of Physic in the Harvard Medical School, will give a medical clinic. To it are cordially invited practitioners and medical students. These clinics will be repeated on Thursdays until May.

On Saturdays in the wards of the Peter Bent Brigham Hospital, from 10 to 12, staff rounds will be conducted by Dr. Christian. These are open to all physicians.

REPORTS AND NOTICES OF MEETINGS

CANCER CONFERENCE AT THE LYNN HOSPITAL

On January 11, 1935, the customary monthly staff conference was taken over by the Lynn Cancer Clinic. To this conference all physicians were invited.

Dr. George A. Leland, Jr., of Boston, acted as consultant to the clinic and was introduced by Dr. William T. Hopkins, chairman of the Lynn Cancer Committee, which operates the clinic.

A brief review of the organization and set-up of the clinic was given and a report made that, after seven and three-quarters years of activity, the clinic is able to report 105 five-year cures, which comprise not only skin cancers which, of course, preponderate, but also cancers of the breast, uterus, colon, stomach, scrotum and other organs. It was pointed out that this would appear to demonstrate that despair is not a reasonable attitude for the person afflicted with cancer, since present statistics indicate that of the five-year cures 89 per cent remain permanently relieved of the disease. During the year 1934, 413 patients applied to the clinic for advice. Of these ninety-two were found to have cancer and two Hodgkin's disease. Forty of the cases having cancer were referred by physicians.

Dr. Leland demonstrated methods of diagnosis and described the standard operation for radical removal of cancer of the breast, paying a graceful tribute to Dr. Robert B. Greenough whose outstanding work in this field is so well known.

The cancer clinic is conducted each Friday morning at 10 o'clock at the Lynn Hospital.

THE ADEQUACY OF MEDICAL CARE IN MASSACHUSETTS

At the joint meeting of the Public Relations Committees of the Essex North and South, and Middlesex East and North Districts held at Shawsheen Manor on January 16, 1935, at 4 P.M., the survey of the adequacy of medical service in Massachusetts was considered.

It was unanimously adopted as the sentiment of those present that this survey is definitely worthwhile. It was further unanimously adopted that the district Public Relations Committees were neither fitted by experience nor by the very limited financial resources of the District Societies to carry on this work. It was, therefore, resolved that the Public Relations Committee of the State Society be urged to finance and undertake the work.

M. A. TIGHE, M.D., *Chairman*,
E. S. BAGNALL, M.D., *Secretary*.

January 18, 1935.

THE BROOKFIELD MEDICAL CLUB

The Brookfield Medical Club held its 520th meeting at the Hampshire House, Ware, Mass., with Dr. A. H. Petit of Ware, host, and Dr. James T. Brosnan of Worcester, speaker. His subject was "The Management of Nephritis."

The February meeting will also be held in Ware at the Hampshire House, February 20, when Dr. Ralph Miller of Ware will entertain the club. The speaker on that occasion will be Dr. O. K. Menard, formerly of the Lahey Clinic in Boston, now located in Springfield. His subject will be "Allergy in General Practice."

J. R. FOWLER, M.D., *Secretary*.

NEW ENGLAND ROENTGEN RAY SOCIETY

A meeting of the New England Roentgen Ray Society was held at the Boston Medical Library on the evening of December 21. Dr. Donald S. King of the Massachusetts General Hospital spoke on "The Lateral X-ray Film in the Diagnosis of Pathology in the Region of the Middle Lobe." After a brief review of the anatomy of the middle lobe of the right lung together with a summary of the important points to consider in examining the x-ray films, Dr. King discussed a long series of interesting slides illustrating conditions in the region of the middle lobe. Slides of an abscess in the middle lobe in both anteroposterior and lateral views were shown. In the case of pneumonic consolidation of this lobe which he demonstrated, the right border of the heart was obscured. The lateral film is particularly important in the diagnosis of atelectasis of the middle lobe.

Cases of tumor in this region were also shown, as well as slides taken of patients with an obstruction in the bronchus of the middle lobe, and post-empyemic fibrosis, and in all these cases the use of the lateral view was well demonstrated. In collapse of the lower two lobes on the right side, there is a typical dense shadow in the cardiophrenic angle. In interlobe effusion between these two lobes there is a definite spindle-shaped shadow which gradually becomes triangular as the pus or effusion clears. Dr. King has found no cases of uncomplicated empyema in this locality. In this condition the anteroposterior view often shows surprisingly little pathology.

In a discussion of the differential diagnosis between bronchiectasis of the middle and lower lobes, he said that the lateral film often does not help and that a lipiodol injection is necessary. One case of "dry bronchiectasis" in a small area in the lower lobe was shown, where repeated hemorrhages in spite of the negative lipiodol findings made operation with lobectomy essential.

Several cases were shown where there was an overlap of the diaphragmatic and heart shadows which has been confused with a spindle-shaped shadow in the region of the middle lobe. The right diaphragm may be displaced upward by a tumor in the liver thus simulating a pulmonary tumor of the right lower lobe. A case of middle lobe abscess simulating tumor was presented, as well as one of middle lobe bronchiectasis that was mistaken also for tumor.

In using lipiodol in cases of suspected bronchiectasis, it is best to inject the right side first, take films of that side in the lateral view, and then inject the left bronchi; otherwise the lateral shadow may be confusing due to the overlap of the two sides in that view.

Dr. King then presented a few additional slides that he thought might be of interest. The first case was that of a man with suspected carcinoma of the testicle with a pulmonary metastasis. Because Dr. Holmes would not treat the lung condition by deep x-ray therapy until the diagnosis had definitely been established, the testicle was removed and found to be a gumma. The lung completely cleared when antiluetic treatment was instituted.

The second case was that of a hypernephroma of the kidney with a single metastasis to the lung. The kidney was removed and after preliminary x-ray treatment to the lung, the metastasis was also removed. During the eighteen months which have elapsed since the operations, there has been no recurrence. Another case with a benign adenoma of the bronchus was presented in which there were resulting atelectasis and numerous bronchiectatic cavities. This patient is to be operated upon for radical removal of the affected lobe. The next case was one with pneumothorax treatment of a severely infiltrated tuberculous lung, which after prolonged and complete collapse showed calcification of the pleura and failure to reëxpand. Another case of tuberculosis of the lung was shown where a very small lesion had been missed and later went on to cavitation.

In the discussion which followed, Dr. Holmes emphasized the importance of the x-ray man keeping in touch with the clinician. He said that the stereoscopic views do not replace lateral films. It is most important to have a definite pathological diagnosis made of any lesion before the roentgenologist consents to treat it, as otherwise considerable damage may be done. The Massachusetts General Hospital has had no success in the x-ray treatment of hypernephroma.

In answer to a question of Dr. Butler concerning the accurate localization of pus and telling the surgeon where to tap, Dr. King said that the surgeon should be allowed to find the pus himself, although the right rib can usually be told by x-ray. Dr. Sosman confirmed the general opinion in that he has never seen interlobar empyema without abscess. He brought up the question of confusing the right inferior accessory lobe with middle lobe pathology, especially as these small areas at the right base near the heart shadow are present in ten per cent of all people and are very prone to become diseased. Dr. Sosman said that at the Peter Bent Brigham Hospital they depend more on fluoroscopy to localize pathology in the right lung than on the lateral film, but Dr. Holmes feels that lateral views are very important, as much may be missed in fluoroscopy alone in this view.

After a brief discussion of a case of supposed congenital cystic disease of the lung, Dr. Vogt said that the disease is very rare at the Children's Hospital and that most cases are probably really only emphysematous blebs. He also pointed out that he has seen several cases of primary interlobar empyema in children and that he believes the abscess is secondary to the empyema rather than vice versa. Dr. King said that all of the cases that he had seen were post-tonsillectomy and that he had assumed therefore that they were secondary to the abscess. Dr. Holmes advised taking plates in both expiration and inspiration and said that he questioned whether there is any such condition as congenital pulmonary cystic disease.

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists was held on the evening of December 19, 1934 at the Harvard Biological Laboratories in Cambridge.

Dr. G. P. Grabfield read a paper on "A Study of Urinary Albumin with Reference to Its Sulphur Content." The especial features set forth are as follows: In normal urine the nitrogen to sulphur ratio is from fourteen to eighteen to one. There are two groups of patients with Bright's disease: those showing massive edema with a high serum cholesterol, a low serum protein, and an excretion of from 40 to 60 Grams of albumin per day in the urine; and those who show primarily the glomerular type of kidney damage and a much lower protein excretion.

In the first or nephrotic type the patients are always in a positive nitrogen and sulphur balance and the excretion of these two elements is in the ratio of from 20 to 30 to one, there being a marked retention of sulphur. In the glomerular type of kidney disease the nitrogen-sulphur ratio is below normal, often being as low as ten to one.

The protein precipitated from the urine in patients with the nephrotic syndrome contains only six hundredths of one per cent of sulphur or a protein-sulphur ratio equal to 259. This determination was checked on the dried protein and by dialysis and was found to be correct. The results were obtained by subtracting the determinations on the filtrate after precipitation from those on the whole urine as voided.

Doctor Grabfield then discussed the nitrogen-sulphur ratios in various conditions. In hyperglobulinemia it is 13, in cardiac edema 16 to 18, in the toxemia of pregnancy 16 to 18, in mercury poisoning which affects the tubules it is 10. The nephrotic type of kidney disease was the only condition studied in which the ratio was very definitely high, often being over 100.

When urea is fed to the nephrotic patient, the urea excretion rises and the sulphur excretion is distinctly diminished, while in glomerular types of nephritis the administration of urea has no effect on the nitrogen-sulphur ratio.

Dr. D. McK. Rioch spoke on "Certain Cortico-Thalamic Relationships Observed in Decorticate Cats." He briefly reviewed the clinical effects of such operations. All showed sham rage on handling. Microscopic slides through the central thalamic region of the four cats were shown. There was an extraordinary degeneration of the thalamus with a complete dropping out of the ganglion cells as well as the ventral and lateral thalamic nuclei. The nucleus reticularis was preserved, indicating that there are descending fibres and an efferent function of the thalamus. The hypothalamus was well preserved.

The lateral geniculate probably sends fibres to the thalamus as well as to the cortex and possibly to the mesencephalon. The cortex and thalamus are essentially one functional system, so that lesions of the cortex cause degeneration of the thalamus and vice versa.

Dr. N. F. Conant spoke on "The Dermatophytes." These are parasitic fungi which present different characteristics when cultured on artificial media than they do in the skin lesions. Numerous slides of the different types were shown. The trichophytons attack the hair, trichophyton endothrix forming spores in chains entirely within the hair shaft, while trichophyton ectothrix forms spores in chains both within and without the hair shaft in parallel arrangement. These types do not mix in the same patient. The spores in artificial media such as cereal grain and water or polished boiled rice may be blunt at both ends and multicellular. In another type there may be cup-shaped lesions all over the body in which a hair shaft forms the center and the hair shows large air spaces in the shaft.

The epidermophyton often gives inguinal lesions in which the scrotum is frequently involved. In this type there are clusters of multicellular macrospores which are club-shaped and which are attached in sessile fashion. In the microsporon infection there is usually a "ringworm" effect with an active border and a quiet center. A grey, heavy sheath is formed around the hair and the arrangement of the spores is like a mosaic. The different types of microsporon spores were described.

There are two aspects to these fungi: first, the parasitic, and secondly, the saprophytic which is best seen in artificial culture media. The difficulty of establishing effective treatment varies considerably with the different species. In the types attacking the hair, epilation is necessary.

NEW ENGLAND OPHTHALMOLOGICAL SOCIETY

A meeting of the New England Ophthalmological Society was held December 18, 1934 at the Massachusetts Eye and Ear Infirmary. After the business meeting, Dr. E. B. Dunphy presented a case of intermittent exophthalmos in a boy of nineteen. For the past year whenever this patient has exerted himself or lain on his left side, his left eye has become more prominent. Physical examination was essentially negative except for a definite enophthalmos on the left side which was compensated for when any of a series of procedures to raise the venous pressure was carried out. Thus bilateral jugular compression caused the compensatory exophthalmos while unilateral compression did not. In the four autopsies on the sixty reported cases of this condition, varicose veins of the orbit were found in all. The condition is probably congenital.

Dr. William D. Rowland then presented two cases of hysterical blindness. The first case was that of an eighteen year old college girl who suddenly became totally blind after a slight kick in the side of the head while watching a gymnastic stunt. Her sight returned nine days after the accident. The second case was that of a thirty-five year old Italian laborer who suddenly became blind after a seven foot fall in 1929. By all the ordinary tests he was totally blind, had a ptosis of the lids, was unable to open or close his lids, and slept with his eyes open. After many negative physical examinations, he was advised to return to Italy in 1931 where he slowly and completely recovered his sight.

Dr. Henry M. Emmons spoke on "The Development of the Organ of Vision from Its Lowest Form up to the Eye of the Primates." After a brief discussion of the principles of life and protoplasm and the possibility of a law governing the rhythmic changes of the protoplasmic colloids, Dr. Emmons began the main part of his lecture by pointing out that we can see only one out of the fifty-five octaves of light.

In many of the protozoa and metazoa light sensitivity is a property of the body as a whole, while

it is only in the higher animals that there are specialized cells connected by nerves to the central nervous system. This sense is most complicated in man. Fossil remains reveal the fact that in this complex evolution higher efficiency has been secured by increased size on the one hand and specialization of cells on the other.

The most primitive organ of sight is perhaps the rod-shaped structure in certain body surface cells which is stimulated by certain light waves. These "visual rods" may be scattered over the body surface or grouped to form primitive eyes. The surface layer of some animals contains other light sensitive cells. Pigment is usually found in visual cells. The function of an eye is first, to appreciate the intensity of the light; secondly, to determine the relative position of the light; and thirdly, to perceive images.

In certain of the lower animals, in particular the crustaceans, the visual cells secrete a protective covering for the eye consisting of chitinous, colorless material which also acts as a cornea and lens. The eye spot of the mollusc is the simplest type and consists of a series of long, columnar cells with collections of pigment distally and an overlying transparent thickening which acts as a lens. The next step in the evolutional development of the eye is seen in the starfishes where a second type of cell serves as a supporting structure. In these forms of life the light perceiving cells are connected to prolonged nerve fibers and in certain species the eye is a cup-like hollow lined by pigmented visual cells and supporting a flat lens.

Planarians have single eye cells with one drawn out nervous connection and they are usually sunk below the surface without a lens. In some of the urchins there are a number of visual units, each of which has a pigment cup at its proximal end and a cap of several cuboidal cells.

As we go up the animal scale there are three stages through which one passes to arrive at true vision. The first of these, phototropism, is purely protective and causes the animal to move as a whole toward or away from light. The second stage is sensation and the third is specific sensation in which light is recognized as such by the animal.

The cup-shaped eyes of some of the lower animals have a narrow opening which in a slightly higher stage becomes closed and covered with a surface epithelium, as in spiders. Many of the crustacea have compound eyes made up of numerous units each of which is a complete eye. There are three stages in the development of the vertebrate eye: first, the development of the surface ectoderm; secondly, the eye sinks down to lie next to the medullary canal; and thirdly, the eye grows out again to take up a surface position.

Dr. Emmons closed his talk by pointing out certain interesting facts: there is no movement of the eyes of invertebrates; all fishes are color blind; snakes can see only objects in motion; birds have a visual acuity one hundred times that of man; there is no stereoscopic vision below the apes; there is a nictitating membrane in man; and the cat family, except the larger species, have vertical pupils.

Dr. A. S. Begg briefly discussed the paper and pointed out that there is no definite rule to follow in the evolutional development of the eye, there being very complex eyes in certain invertebrates and very simple eyes in some of the vertebrates. Evolution in this respect represents a series of natural experiments with certain features common to all. He spoke on the development of the cerebral eye. Embryonically it is associated with the neural crest, being represented by a pitting at the anterior end of this crest. Later an evagination takes place to form the eye bud, and the surface is indented to show where the optic cup will be. In the seven millimeter embryo the lens vesicle is closed off, the optic cup is inverted, the lens pushed back from the surface, nerve fibers develop, and the retina with its pigment cells is formed. The bud carries with it cells that later become sensory cells, others that become supporting cells, while the outer layer of the cup forms the pigment cells.

BOSTON CITY HOSPITAL SURGICAL CLINIC

Surgical Clinic, Boston City Hospital, Friday, February 1, 12-1, in the Cheever amphitheatre.

Dr. William R. Morrison, Associate Professor of Surgery, Boston University School of Medicine, will present:

1. A case of perforated ulcer of stomach.
2. A case of aneurysm of axillary artery and aneurysm of the thoracic aorta.
3. In addition, certain acute surgical cases will be presented for discussion.

Physicians and medical students are invited.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The next meeting of the New England Dermatological Society will be held on Wednesday, February 13, at 3 P.M. at the Massachusetts General Hospital.

J. HARPER BLAISDELL, M.D., *Secretary.*

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, JANUARY 28, 1935

Monday, January 28—

*8:15 P.M. New England Heart Association. Beth Israel Hospital, Boston.

Tuesday, January 29—

1:30 P.M. Radio Program. WEEI. "Water Purification."

†2:30-4 P.M. Ward visit, Massachusetts Eye and Ear Infirmary.

†4-5 P.M. Seminar, Pediatric Laboratory, Massachusetts General Hospital.

4:30 P.M. Radio Program. WBZ. "Stomach and Duodenal Ulcers."

Thursday, January 31—

*12 M. Clinico-Pathological Conference. Massachusetts General Hospital.

†12 M. Clinico-Pathological Conference. Children's Hospital.

*3:30 P.M. Medical Clinic. Dr. Christian. Peter Bent Brigham Hospital.
†4:30 P.M. Surgical Clinic. Children's Hospital Amphitheatre.

Friday, February 1—

†12 M. Clinical Meeting of Children's Medical Staff, Massachusetts General Hospital. Ether Dome.
*12-1 P.M. Boston City Hospital. Surgical Clinic. Cheever Amphitheatre.
5:00 P.M. Radio Program. WEEI. "Pasteurization of Milk. Protection of Ice Cream."

Saturday, February 2—

*10-12. Medical Staff Rounds. Dr. Christian. Peter Bent Brigham Hospital.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society.

January 25 and 26—New England Roentgen Ray Society. See page 133, issue of January 17.

January 29—New England Heart Association will meet at the Beth Israel Hospital, Boston, at 8:15 P.M.

January 31—Clinic at the Peter Bent Brigham Hospital. See page 176.

February 1—Boston City Hospital Surgical Clinic. See page 179.

February 8—William Harvey Society. Dr. Arthur M. Fishberg, New York City, will speak on "Peripheral Vascular Collapse."

MASSACHUSETTS DIETETIC ASSOCIATION

February 12—Tuesday, 8 P.M. "Diabetic Children," Dr. Priscilla White, Joslin Diabetic Unit.

March 12—Tuesday, 8 P.M. "The Effect of Diet on Anemia," Dr. Lewis Diamond, Instructor in Medicine, Harvard University Medical School, Associate Physician, Children's Hospital.

March 19—Tuesday, 2 P.M. Field Trip: Visit Storehouse, First National Stores.

April 9—Tuesday, 8 P.M. "Small Hospital Problems," Miss Margaret Copeland, Superintendent, Free Hospital for Women.

February 13—New England Dermatological Society. See page 179.

February 20—Brookfield Medical Club. See page 176.

March 11, 12, 13—Surgeons to meet in Jacksonville, Florida (Southeastern Surgical Congress). See page 83, issue of January 10.

April 29 - May 3, 1935—The American College of Physicians will meet at Philadelphia. For information address Mr. E. R. Loveland, Executive Secretary, 133-135 South 36th Street, Philadelphia, Pa.

June, 1935—Medical Library Association will meet in Rochester, N. Y. For details address the Secretary: Miss Frances N. A. Whitman, Librarian, Harvard University Schools of Medicine and Public Health, Boston, Mass.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The Annual Meeting will be held in May. Time, place and subject to be announced.

E. S. BAGNALL, M.D., Secretary.

FRANKLIN DISTRICT MEDICAL SOCIETY

Meetings will be held on the second Tuesday of March and May at the Weldon Hotel, Greenfield, Mass.

CHARLES MOLINE, M.D., Secretary.
Sunderland.

MIDDLESEX EAST DISTRICT MEDICAL SOCIETY

March 13, 1935—Wakefield.
May 8, 1935—Winchester.

K. L. MACLACHLAN, M.D., Secretary.
1 Bellevue Street, Melrose.

NORFOLK DISTRICT MEDICAL SOCIETY

January 29, 1935—Hotel Kenmore, 8 P.M. The Compression Treatment of Tuberculosis, Including Pneumothorax, Phrenicectomy and Thoracoplasty. Drs. Richard H. Overholt, N. R. Pillsbury and Hugh Hare.

February 26, 1935—Hotel Kenmore, 8 P.M. The Use of Amniotic Fluid in Abdominal Surgery. Dr. Herbert L. Johnson.

March 26, 1935—Fernald School for Feeble-Minded, Waverley. Details to be announced.

May, 1935—Annual Meeting. Date, time and place to be announced.

PLYMOUTH DISTRICT MEDICAL SOCIETY

March—Plymouth County Hospital.
April—Lakeville Sanatorium.

SUFFOLK DISTRICT MEDICAL SOCIETY

March 27, 1935—Clinical Meeting at the Boston Lying-In Hospital.

April 24, 1935—Clinical Meeting at the Children's Hospital.

The medical profession is cordially invited to attend all of these meetings.

ROBERT L. DeNORMANDIE, M.D., President.
GEORGE P. REYNOLDS, M.D., Secretary.

WORCESTER DISTRICT MEDICAL SOCIETY

February 13, 1935—Wednesday evening. Worcester State Hospital, Worcester, Mass. 6:30 P.M.: Dinner. 7:30 P.M.: Scientific program and business session. Announcement of subjects and speakers to be presented at a later date. Dinner complimentary by the Hospital.

March 13, 1935—Wednesday evening. The Memorial Hospital, Worcester, Mass. 6:30 P.M.: Buffet supper. 7:30 P.M.: Scientific program and business session. Announcement of subjects and speakers to be presented at a later date. Buffet supper complimentary by the Hospital.

April 10, 1935—Wednesday evening. Worcester Hahnemann Hospital, Worcester, Mass. 6:30 P.M.: Dinner. 7:30 P.M.: Scientific program and business session. Announcement of subjects and speakers to be presented at a later date. Dinner complimentary by the Hospital.

May 8, 1935—Wednesday afternoon and evening. Annual Meeting of the Worcester District Medical Society. The time and place of this meeting will be announced later.

ERWIN C. MILLER, M.D., Secretary.
27 Elm Street, Worcester.

BOOKS RECEIVED FOR REVIEW

Sculpture in the Living. Jacques W. Maliniak. 203 pp. New York: The Lancet Press. $3.00.

The Vitamin B Requirement of Man. George R. Cowgill. 261 pp. New Haven: Yale University Press. $4.00.

Surgical Applied Anatomy. Sir Frederick Treves. Ninth Edition, Revised by C. C. Choyce. Illustrated. 720 pp. Philadelphia: Lea & Febiger. $4.00.

An Atlas of the Commoner Skin Diseases. Henry C. G. Semon and Arnold Moritz. 221 pp. Baltimore: William Wood & Company. $12.00.

How Safe Is Home? Howard Whipple Green. 48 pp. Cleveland: Cleveland Health Council. 50 cents.

Body Mechanics in the Study and Treatment of Disease. Joel E. Goldthwait, Lloyd T. Brown, Loring T. Swaim, and John G. Kuhns. 281 pp. Philadelphia: J. B. Lippincott Company. $4.00.

A Truthtelling Manual and the Art of Worldly Wisdom. Being a collection of the aphorisms which appear in the works of Baltasar Gracian. Translated by Martin Fischer. 287 pp. Springfield: Charles C Thomas. $3.00.

Anaesthesia and Analgesia in Labour. Katharine G. Lloyd-Williams. 96 pp. Baltimore: William Wood & Company. $2.00.

The Treatment of Common Female Ailments. Frederick John McCann. Third Edition. 379 pp. Baltimore: William Wood & Company. $4.75.

Studies from The Rockefeller Institute for Medical Research. Reprints. Volume 91. 598 pp. New York: The Rockefeller Institute for Medical Research, 1934.

The Management of Fractures, Dislocations, and Sprains. John Albert Key, and H. Earle Conwell. 1165 Illustrations. 1164 pp. St. Louis: The C. V. Mosby Company. $15.00.

BOOK REVIEWS

Human Sterility. Causation, Diagnosis, and Treatment. By Samuel Raynor Meaker. 27 illustrations. 276 pp. Baltimore: The Williams & Wilkins Company. $4.00.

This is a book for the specialist and one that will repay his careful study. It is the eighth in a series on the Medical Aspects of Human Fertility sponsored by the National Committee on Maternal Health, Inc. The contents are well arranged and the method of presentation clear. Etiology and diagnosis are well treated. These two parts which also include a discussion of endocrinologic investigations as a part of the general diagnostic procedure comprise 204 of the 276 pages. The section on treatment (forty-one pages) is disappointingly brief; that on the results of treatment (eleven pages) very meager indeed. Some bare statistics are given but unfortunately these are not correlated with the statistics given in the section on etiology. The value of the methods of study and of the treatment advocated cannot therefore be evaluated from any data given in the text. A good working bibliography is appended. The book is interesting and well worth reading, but after all is said merely represents the opinions and practice of one small group of collaborators. It is not the comprehensive compilation which we might have expected from the National Committee on Maternal Health.

Diagnostic Clinique. Examens et Symptomes. Par A. Martinet et collaborateurs. 1138 pp. Sixième Édition Entierement Refondue. Paris: Masson et Cie. 145 fr.

The necessity of a sixth edition of this book emphasizes more than the reviewer can describe in words the interest and appreciation of the profession in a well-coördinated, well-written, and comprehensive treatise on clinical diagnosis.

Many additions to the fifth edition, which was published in 1925, have been made. Bronchoscopy and gastroscopy are described and discussed. New procedures such as the visualization of the biliary tract, arteries, and spleen are adequately and thoroughly treated. Many chapters such as the examination of the intrathoracic tract, diagnostic procedures in gastric diseases, heart, electrocardiography, and blood dyscrasias have been completely revised. Genitourinary diseases are fully recorded.

The collaborators have retained the original plan of the book. Part one is devoted to generalities on diagnosis, errors in diagnosis, and how to go about doing a complete medical examination. Part two encompasses the entire field of special examinations, such as those relating to the eye, digestive tract, heart, lungs, blood, genitourinary tract, and nervous system. The second half of the book discusses symptoms under headings such as adenopathy, ascites, edema, icterus, cough and many others.

This edition has 1154 pages and is well illustrated. It is unquestionably one of the best French medical books published, and its usefulness should be unlimited. The treatise is highly recommended.

Cataract. Its Etiology and Treatment. By Clyde A. Clapp. 254 pp. Philadelphia: Lea & Febiger. $4.00.

Lacking direct blood and nerve supply, the crystalline lens is considered to be susceptible only to degenerative changes designated as cataract, which constitutes one of the major problems in ophthalmology. During the past twenty years, the slit-lamp and binocular microscope have thrown more light upon the growth and development and the degenerative changes of the crystalline lens than the combined studies of all preceding time. Biophysicists and biochemists are now delving into the peculiar metabolism of the crystalline lens, to explain the manner in which it maintains transparency, meets its nutritional and oxygen requirements, fulfills its accommodative function, and acts as a selective light filter.

Dr. Clapp's text is timely, well written, amply illustrated, and carries 666 references to important contributions on the subject. The first half of the book gives an excellent résumé of the known embryology, anatomy, physiology, chemistry, and degenerations of the lens, and the second half contains a concise summary of the medical and surgical treatment of cataract and of postoperative complications.

The book deserves a place on the desk and in the attention of every practicing ophthalmologist.

The Practice of Dietetics. L. H. Newburgh and Frances Mackinnon. 264 pp. New York: The Macmillan Company. $4.00.

This is not merely a collection of menus but rather a presentation of methods for deciding whether and how disease may be ameliorated by diet. The subject is divided into three parts. The first deals with the material needs of the organism referring especially to the structural substances, protein and inorganic substances, the sources of energy and the regulating substances. The second part is concerned with the selection of food. In the third part, therapy by means of diet is presented.

The authors feel that pure proteins are harmless, but that since nucleic acid and certain non-protein meat extractives will produce contracted kidneys experimentally, the amount of protein fed in the form of meat is of significance. The selection of proteins for their content of specific amino acids is presented.

The energy exchange of man depends upon the ingestion of potential energy in the form of food. Excessive ingestion of food energy does not increase the transformation of energy, but results in storage of potential energy as fat, with resultant unfavorable effect upon mortality rates.

The authors present a method of calculating the twenty-four hour energy production from carbohy-

drate, protein and fat by utilizing measurements of the insensible perspiration.

Under the regulatory substances, the major part of the discussion is given to Vitamin D and the calcium-phosphorus exchange.

In the Table of Nutritive Value of Foods are included many of the analyses of Lawrence and McCance. The latter attempted to eliminate both cellulose and hemi-cellulose from the final results and obtained figures for "available carbohydrate" in vegetables, fruit and nuts. One objection to their figures is that they examined only six samples of the various foods and it is not stated that the foods were gathered from widely separated regions. The values for carbohydrate, therefore, in some foods, apples, for example, are as much as 50 per cent lower than values previously used. However, the tables have the additional advantage of giving the values for calcium, phosphorus and iron, the relative content of each vitamin and their acid or basic reaction in terms of N/10 HCL.

Newburgh and Mackinnon review the observations upon the metabolism of fasting and undernutrition in diabetes which led to Newburgh's adoption of the low carbohydrate and protein with high fat diet. The publication of these diets in 1923 liberalized the caloric values of diabetic diets generally, but the use of diets containing from 20 to 100 grams carbohydrate nowadays seems at least out of harmony with general practise. Curiously enough, in the severest cases of diabetes, diets of the liberal carbohydrate type are employed to produce hyperglycemia and avoid insulin reactions. This procedure is recommended on the ground that in such cases, all tolerance has been lost anyway, and hyperglycemia does no harm except to reduce tolerance. It has been generally observed that the fatal or crippling complications of diabetes such as carbuncles, infections of the urinary tract, and cataracts occur even in the young with greatest frequency where hyperglycemia is least well controlled.

The authors' statements regarding arteriosclerosis in diabetes are more sweeping than the data available at present should permit. They state that diabetic gangrene is due solely to medial arteriosclerosis, and that this is never produced by means of cholesterol feeding. Medial sclerosis occurs in both diabetics and non-diabetics. The case should rest on pathologic data and more than one pathologist has noted the predominance of the initial atherosclerosis in arteries of diabetic legs.

Treatment of coma is given but slight mention. Twenty units of insulin injected at six hourly intervals seems a dangerous rule to promulgate. It can only mean that the authors have had little personal experience in treating coma, and, in fact, the reviewer does not know of any large series of coma cases reported from their department at the University of Michigan. Altogether the book will be found stimulating and informative in spite of certain glaring inequalities.

Manual of the Diseases of the Eye. For Students and Practitioners. By Charles H. May. Fourteenth Edition, Revised. 496 pp. Baltimore: William Wood and Company. $4.00.

The fourteenth edition of Dr. May's Manual presents much useful information within its 496 pages, and its 376 illustrations many of which are in color. The utility of the book is greatly enhanced by the addition of Dr. Dunnington's chapter on disturbances of ocular motility. The work is valuable as a clinical manual for the beginner.

Ophthalmology is no longer a separate science, or empirical. Yearly it is being recognized that the practitioner who treats eye conditions must widen his knowledge of physics, chemistry, biology, and of clinical medicine in general. To interpret the lesions one finds, and to treat disease intelligently, one must correlate the clinical with the fundamental. Nowadays, even in a manual, one is disappointed if one does not find with each clinical entity descriptions dealing with histopathology, with biochemistry, with the latest advances in bacteriology, and with slit-lamp microscopy.

Medical Art Calendar, 1935. The Hague: J. Philip Kruseman. $2.00.

This calendar, of a good deal of interest to doctors, upholds the standard set in previous years. The reproductions of noted paintings are very well done in brown and most of the material is of distinct medical interest.

Rules for Recovery from Pulmonary Tuberculosis. Lawrason Brown. Sixth Edition, thoroughly revised. 275 pp. Philadelphia: Lea & Febiger. $1.75.

The mere fact that this book of Dr. Lawrason Brown's has reached a sixth edition speaks for itself. Several new chapters have been added including one on the surgical treatment of tuberculosis with remarks on the vitamins, alcohol, tobacco, immunization and rehabilitation. There are 250 pages of rather fine print and there is no doubt but that all the information that any patient may need is contained in this little volume. To the reviewer, at least, the only possible criticism that can be made of Dr. Brown's book is that it contains almost too much information and that in too detailed and technical language. It is to be doubted as to whether it is beneficial for the average patient to make too careful a study of the number of calories that he consumes each day or the exact kind and variety of the vitamins contained in his food. The reviewer accustomed to reading all books of this sort must admit that he finds this one distinctly hard reading. Perhaps if he were a patient and had unlimited time at his disposal it would be easier.

Despite this very minor criticism, however, the book stands for all that is worth while in the treatment of this disease and is bound to increase steadily in usefulness.